Complimentary e-book with digital resources
at www.MedEnact.com

RESPECT COPYRIGHT
ELIMINATE PIRACY

CONCISE ORAL PATHOLOGY

SECOND EDITION



K Manjunath

ELSEVIER

CONCISE ORAL PATHOLOGY

SECOND EDITION

K Manjunath, BDS, MDS

Fellow in Aesthetic Medicine & Cosmetology, Griefwald University, Germany
Managing Director, MEDIDENT Health Care Centres, Mysore, Karnataka, INDIA

ELSEVIER

https://t.me/RoyalDentistryLibrary/

Table of Contents

Cover image

Title page

Copyright

Dedication

Foreword 1

Foreword 2

Contributors

Preface to the second edition

Preface to the first edition

Acknowledgements

1. Developmental disturbances of oral and paraoral structures

- Developmental anomalies of tongue
- Developmental anomalies of oral lymphoid tissue
- Developmental disturbances of salivary glands
- Developmental anomalies of lip

https://t.me/RoyalDentistryLibrary/

Hereditary intestinal polyposis syndrome

Orofacial clefts/cleft lip and palate

Developmental disturbances of the oral mucosa

Developmental disturbances of gingiva

Developmental disturbances of jaws

Developmental disturbances affecting number of teeth

Developmental disturbances affecting the size of teeth

Developmental disturbances affecting shape of teeth

Developmental disturbances affecting the eruption pattern of dentition

Developmental disturbances affecting structure of teeth

Enamel hypoplasia

2. Benign and malignant tumours of the oral cavity

Benign tumours of epithelial tissue origin

Potentially malignant disorders (premalignant lesions/conditions)

Malignant tumours of epithelial tissue origin

Benign tumours of connective tissue origin

Malignant tumours of connective tissue origin

3. Salivary gland pathology

Benign tumours of salivary glands

Malignant tumours of salivary glands

Tumour-like lesions

Other lesions

4. Odontogenic tumours

5. Cysts of the oral and maxillofacial regions

https://t.me/RoyalDentistryLibrary/

6. Bacterial, viral and fungal infections of the oral cavity

- Bacterial infections
- Viral infections
- Fungal infections

7. Diseases of the periodontium

- Healthy periodontium
- Gingival diseases
- Periodontitis

8. Dental caries

9. Diseases of dental pulp and periapical tissues

- Diseases of dental pulp
- Diseases of periapical tissues
- Osteomyelitis

10. Spread of oral infection

11. Physical and chemical injuries of the oral cavity

12. Regressive alterations of the teeth

13. Healing of oral wounds

14. Metabolic disorders

- Diseases of pituitary gland
- Diseases of thyroid gland

https://t.me/RoyalDentistryLibrary/

Diseases of parathyroid gland

Diseases of pancreatic gland

Diseases of adrenal gland

15. Allergic and immunologic diseases

16. Diseases of the bones and joints

Diseases of temporomandibular joint (TMJ)

17. Diseases of the skin

Genodermatoses

18. Diseases of the blood and blood forming organs

Haematopoiesis (haemato—blood, poiesis—production)

Erythropoiesis (erythro—red, poiesis—production)

Diseases involving white blood cells

Diseases involving platelets

19. Diseases of the nerves and muscles

Diseases of nerves

Diseases of muscle

20. Forensic odontology

21. Histochemistry

Glossary

Appendices Index

https://t.me/RoyalDentistryLibrary/

Copyright

ELSEVIER

RELX India Pvt. Ltd.
Registered Office: 818, 8th Floor, Indraprakash Building, 21, Barakhamba Road, New Delhi-110 001
Corporate Office: 14th Floor, Building No. 10B, DLF Cyber City, Phase II, Gurgaon-122 002, Haryana, India

Concise Oral Pathology, 2e, K Manjunath
Copyright © 2017 by RELX India Pvt. Ltd.
Copyright © 2012 by Reed Elsevier India Pvt. Ltd.
All rights reserved.
ISBN: 978-81-312-4877-5
e-Book ISBN: 978-81-312-4932-1

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher' permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.
This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notice

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become

https://t.me/RoyalDentistryLibrary/

necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

With respect to any drug or pharmaceutical products identified, readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of practitioners, relying on their own experience and knowledge of their patients, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of product liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claims made of it by its manufacturer.

Please consult full prescribing information before issuing prescription for any product mentioned in this publication.

Manager–Content Strategy: Nimisha Goswami
Manager–Education Solutions (Digital): Smruti Snigdha
Content Strategist (Digital): Nabajyoti Kar
Sr Manager–Education Solutions: Shabina Nasim
Sr Content Development Specialist: Goldy Bhatnagar
Project Manager: Nayagi Athmanathan
Sr Operations Manager: Sunil Kumar
Sr Production Executive: Ravinder Sharma
Sr Graphic Designer: Milind Majgaonkar

https://t.me/RoyalDentistryLibrary/

Typeset by GW India
Printed in India by Thomson Press India Ltd., Faridabad, Haryana, India

https://t.me/RoyalDentistryLibrary/

Dedication

Dedicated to

My Mentor

Dr TR Saraswathi

My Parents

Mr V Krishnappa and Mrs N Nalini

My Wife

Dr Nagamani Manjunath

My Son

M Tanish

My Daughter

M Srinika

https://t.me/RoyalDentistryLibrary/

Foreword 1

Dr B Sivapathasundharam, MDS, Professor and Head, Department of Oral Pathology, Meenakshi Ammal Dental College, Chennai, Tamil Nadu

Oral pathology is an important speciality of dentistry, which deals with the identification, cause and behaviour of diseases of oral and maxillofacial region. It forms one of the basic subjects, and spreads to two years in the undergraduate curriculum. Though there are a number of well-written textbooks available, this book intends to help the students for examination preparation.Unnecessary data and references, which confuse the undergraduate students, are not included in this book.

This book is designed in such a way that it covers all the major topics in oral pathology in a concise manner. Each chapter besides containing an introduction covers all aspects of the disease processes in a well-structured format for easier understanding by the BDS students. Point by point presentation of the text helps the students to remember facts easily. Students always prefer line diagrams rather than photomicrographs for their easy reproducibility. Line diagrams, flowcharts and tables in this book add more value.

Besides the preparatory manual for undergraduate students, I hope this book will also serve as a ready-reckoner for the postgraduates of allied specialities and practising dentists.

Foreword 2

Dr A Einstein Thiruselvan Bertin, MDS, Professor and Head, Department of Oral Pathology and Microbiology, Rishiraj College of Dental Sciences and Research Centre, Pipalner road, Gandhinagar, Bhopal, Madhya Pradesh

It is indeed a pleasure to write the Foreword for a gallant effort by a young and aspiring academician, ever zealous to promote the interests of undergraduate students of dentistry in India. Faced with a battery of extensive, redundant and irrelevant literature in the form of postgraduate level textbooks on oral pathology, the undergraduates have so far found oral pathology to be a dreaded subject that is neither comprehensible nor brief.

This book by Dr K Manjunath is a simple-to-read text on oral pathology that serves the requirements for the undergraduate examinations conducted by the dental institutions in India. Plausible explanations, question and answer (Q&A) pattern, schematic illustrations/charts, hand-drawn histology images, and the like, make it an easy read for the students of the undergraduate level. I am more impressed with the manner in which postgraduate level concepts like pathogenesis of lesions are explained in an uncomplicated method, with adequate references. Thence, I believe it would be prudent for the student pursuing MDS in Oral Pathology and Microbiology to have this book as a ready-reckoner at all times.

I wish this effort the success it deserves and hope the goal of making Oral Pathology as a subject easy-to-approach, understand and reproduce is achieved by the author.

Contributors

Degala Nagamani, MDS, Department of Oral and Maxillofacial Surgery, Managing Director, MEDIDENT & D Care Health Care Centres, Mysore, Karnataka, India

B Sabarinath, MDS, Department of Oral Pathology, and Microbiology, Meenakshi Ammal Dental College and Hospital, Chennai, India

Shruthi D Nayak, MDS, Department of Oral Pathology, Yenepoya Dental College, Mangalore, Karnataka, India

K Roopavathi, MDS, Department of Oral Pathology, Vydehi Institute of Dental Sciences, Bangalore, Karnataka, India

Bhushan Sharma, MDS, Department of Oral Pathology and Microbiology, Christian Dental College, Ludhiana, Punjab, India

Gayathri Ramesh, MDS, Department of Oral Pathology, Rama Dental College and Research Center, Kanpur, Uttar Pradesh, India

A Vikram Simha Reddy, MDS, Department of Oral Pathology, G Pulla Reddy Dental College, Kurnool, Andhra Pradesh, India

Ramesh Tatapudi, MDS, Department of Oral Medicine and Radiology, Vishnu Dental College, Vishnupur, Kovvada Village, Bhimavaram, Andhra Pradesh, India

S Shabana Fathima, MDS, Department of Oral Pathology and Microbiology, Sri Venkateshwara Dental College and Hospital, Ariyur, Puducherry, India

Preface to the second edition

K Manjunath

This edition of the book provides a concise version with all the essential aspects of oral pathology. The basic information is given in an accessible format, easy to comprehend and point-wise manner with four-colour hand-drawn histopathological diagrams, flowcharts, tables and schematic illustrations. This would not only make it easier for the students to understand the subject in a simplified manner, but would also help them to quickly review and revise the subject before examination. It also helps those who wish to attain a good knowledge about the nature, identification and behavior of the various oral diseases.

The simple explanations provide better insight towards the subject even for mediocre students. The list of questions in each chapter gives an idea to the students regarding possible ways of asking questions from respective topics in the examination. The hand-drawn histopathology diagrams emphasize the diagrammatic representation of the microscopic features of the oral lesions to construe themselves better in examinations and preparing practical records.

In addition, complimentary access to online frequently asked questions and answers along with full e-book is also provided.

I welcome suggestions from readers to update this book in further editions.

Preface to the first edition

K Manjunath

This book is written to bring out a concise, easily understandable resource for students to learn all the essential aspects of oral pathology and guide them to write well-structured answers in their examinations. It also helps those who wish to attain a good knowledge about the nature, identification and behavior of the various oral diseases.

This book is designed in a well-structured format, especially for undergraduate students with a comprehensive exam-oriented description of oral diseases. This concise book is intended to help students to understand and remember every important aspect of oral pathology in a simple manner. This book covers every important aspect of oral pathology in concise format, which gives a better insight towards the subject even for mediocre students. The simple explanations provide better clarity towards the subject. The list of questions in each chapter gives an idea to the students regarding possible ways of asking questions from respective topics in the examination. The hand-drawn histopathology diagrams emphasize the diagrammatic representation of the microscopic features of the oral lesions to construe themselves better in examinations and preparing practical records. Flowcharts, tables and schematic illustrations help students to interpret their hard work in examinations in a shorter period of time.

I welcome suggestions from readers to update this book in further editions.

Acknowledgements

My deep gratitude, respect and love to Master Choa Kok Sui and Lord Mahaguruji Mei Ling for their beloved blessings.

I wish to thank Dr S Hemavathi, Dr CR Ramachandran, Dr B Kavitha, Dr Usha Hegde, Dr Ashith Acharya, Dr Govind Rajkumar, Dr Ravikanth Manyam and Mr Katta Sathyanarayana for their constant support in completing this book.

A special thanks to my family members, Mr V Krishnappa, Mrs N Nalini, Mrs Nagarathnamma, Dr K Roopa, Dr Sreenivas Venkataram, Ms Shriya, Mrs K Shilpa, Mr TS Bharath, Mr Avyukth.

CHAPTER 1

Developmental disturbances of oral and paraoral structures

Genetics

Terms

- **DNA:** Deoxyribonucleic acid—basic genetic material found in most eukaryotes and some prokaryotes.
- **RNA:** Ribonucleic acid—genetic material of certain viruses and transcripts of DNA in eukaryotes.
- **Gene:** A gene is a segment of DNA that codes for a specific protein.
- **Allele:** An alternate form of a gene.
- **Homozygous:** Individuals carrying identical alleles of a given gene.
- **Heterozygous:** When two different alleles are present in a gene pair, the individual is said to be heterozygous.
- **Dominant trait:** Dominant traits are expressed in the heterozygous condition.
- **Recessive trait:** Recessive traits are expressed only in the homozygous condition.
- **Penetrance:** Penetrance is the probability that a disease will appear in an individual when a disease allele is present.
- **Expressivity:** Expressivity, on the other hand, refers to the range of symptoms that are possible for a given disease.

Pedigree chart

A pedigree chart is a diagram that shows the occurrence and appearance or phenotypes of a particular gene or organism and its ancestors from one generation to the next generation.

The word *pedigree* is derived from the French word *pied de grue* meaning crane's foot, because the typical lines and split lines (each split leading to different offspring of the one parent line) resemble the thin leg and foot of a crane.

Notations

- Roman numerals (I, II, III, etc) symbolize generations.
- Arabic numerals (1, 2, 3, etc) symbolize birth order within each generation.
- In this way, any individual within the pedigree can be identified by the combination of two numbers (i.e. individual II3).

Autosomal inheritance

Autosomal dominant inheritance (fig. 1.1)

- One mutant allele is required to express the mutant phenotype.
- Dominant trait will be expressed in all generations.
- Every affected individual has at least one affected parent.
- Two affected individuals may have unaffected children.
- The trait is passed from the affected parents to about 50% of his/her children.
- Both males and females can transmit the trait.
- *Examples:* Cleidocranial dysostosis, van der Woude syndrome, neurofibromatosis.

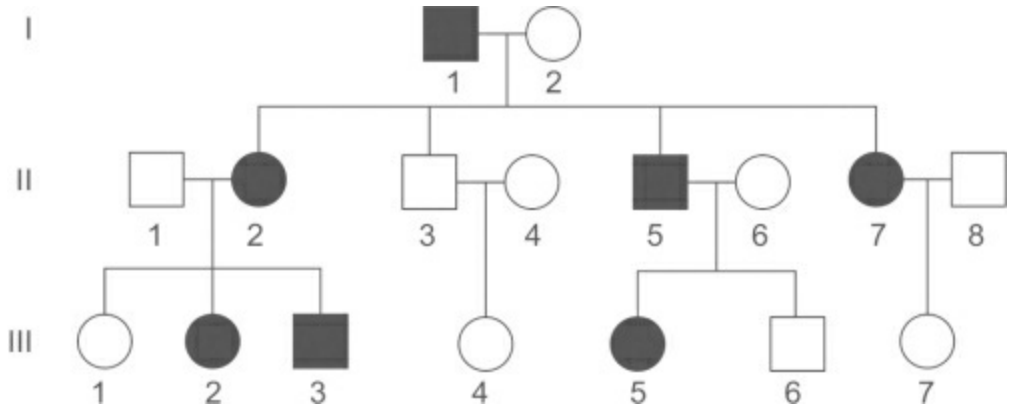
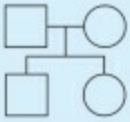
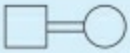


FIG. 1.1 Autosomal dominant inheritance.

Box 1.1

Pedigree symbols

1.		Male
2.		Female
3.		Mating
4.		Parents and siblings
5.		Dizygotic twins
6.		Monozygotic twins
7.		Consanguineous marriage
8.		Unknown sex
9.		Affected male
10.		Affected female
11.		Dead
12.		Carrier
13.		Stillbirth
14.		Proband/propositus
15.		Male heterozygote for recessive allele
16.		Female heterozygote for recessive allele

Autosomal recessive inheritance (fig. 1.2)

- Two mutant alleles are required to express the mutant phenotype.
- It can be expressed only in homozygous individuals.
- 25% of the children will express the trait.
- Both males and females can transmit the trait.
- Consanguinity significantly increases the risk of manifesting a recessive

phenotype.
- *Examples:* Ellis van Creveld syndrome and sickle cell anaemia.

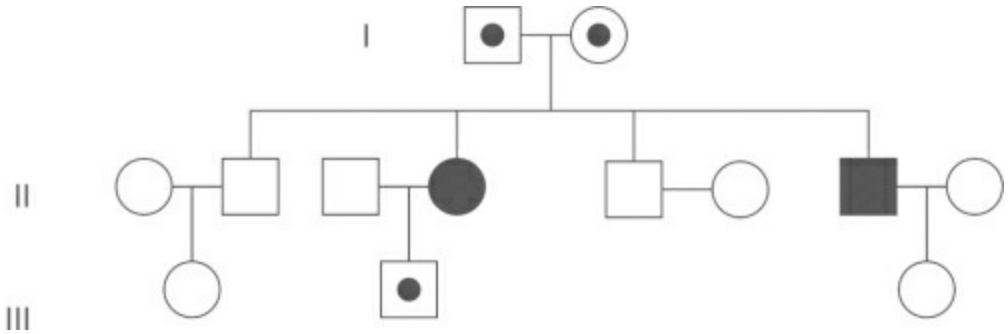


FIG. 1.2 Autosomal recessive inheritance.

Sex-linked inheritance

X-linked inheritance

- X-linked diseases are those for which the gene is present on the X chromosome.
- Males have one copy of the X chromosome (plus their Y chromosome) and females have two X chromosomes.
- *Male: Hemizygous*—with respect to X chromosome.
- *Female: Homozygous*—with respect to X chromosome.
- The characteristics that are common to X-linked disorders include:
 - X-linked genes are never passed from father to son.
 - The Y chromosome is the only sex chromosome that passes from father to son.
 - Males are never carriers—if they have a mutated gene on the X chromosome, it will be expressed.
 - *Example:* Haemophilia.

Y-linked inheritance

- Inheritance of genes on the Y chromosome.
- Since only males normally have a Y chromosome, Y-linked genes can only be transmitted from father to son.
- Y-linked inheritance is also called *holandric* inheritance.
- A number of genes were known to be Y-linked including:

- SRY—Sex determining region on Y-chromosome.
- *Example:* Hypertrichosis of the pinna of the human ear.

X-linked dominant inheritance (fig. 1.3)

- Females are more frequently affected than males, and the chance of passing on an X-linked dominant disorder differs between men and women.
- Families with an X-linked dominant disorder often have both affected males and affected females in each generation.
- A striking characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).
 - *Example:* Incontinentia pigmenti.

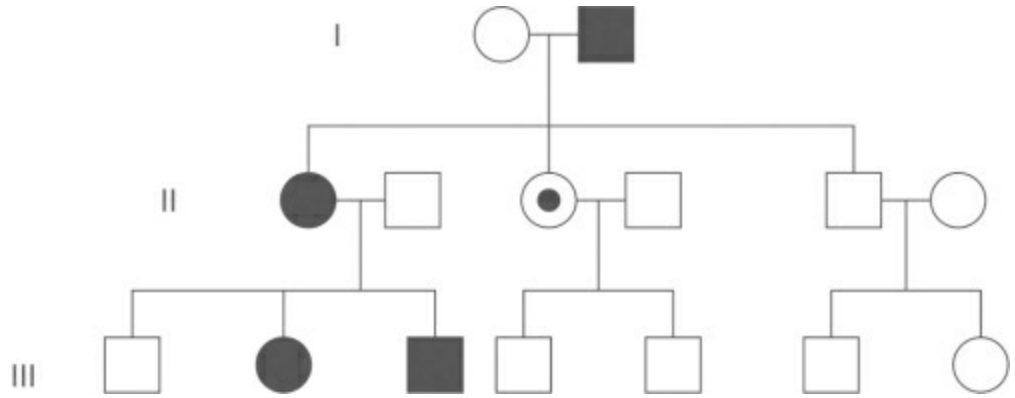


FIG. 1.3 X-linked dominant inheritance.

X-linked recessive inheritance (fig. 1.4)

- X-linked recessive disorders are caused by mutations in genes on the X chromosome.
- Males are more frequently affected than females, and the chance of passing on the disorder differs between men and women.
- Males cannot be carriers.
- Females are most often carriers or exhibit a mild form of the disease.
- Families with an X-linked recessive disorder often have affected males, but rarely affected females, in each generation.
- A striking characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).
 - *Example:* Haemophilia.

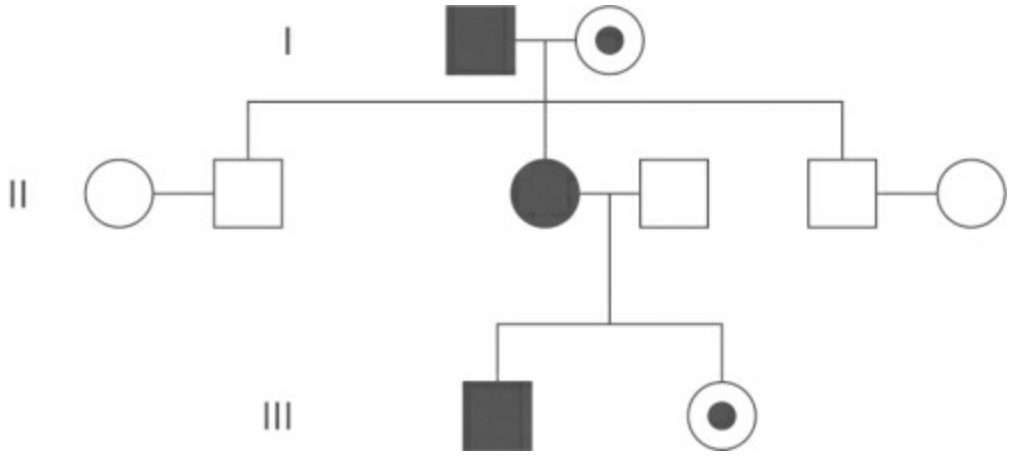


FIG. 1.4 X-linked recessive inheritance.

Developmental anomalies of tongue

Microglossia

(Synonym: Hypoglossia)

- It is a small or rudimentary tongue.
- It is an uncommon developmental condition, associated with severe dentoskeletal malocclusion.
- It is often associated with *oromandibular limb hypogenesis syndrome.*
 - Limb anomalies: Hypodactylia (absence of digits)
 - Hypomelia: Hypoplasia of part or all of a limb
- Some patients may be associated with cleft palate and intraoral bands.

Macroglossia

(Synonyms: Tongue hypertrophy; prolapsus of the tongue)

- Enlargement of the tongue.
- It is caused by a wide variety of conditions including both congenital malformations and acquired diseases.

Classification

- *True macroglossia.* It can be either congenital (Beckwith–Wiedemann syndrome, Down's syndrome) or acquired (tuberculosis, acromegaly, haemangioma, amyloidosis).
- *Relative macroglossia/pseudomacroglossia:* Due to insufficient space in the oral cavity, the tongue is forced to sit in an abnormal position. The various conditions which lead to pseudomacroglossia include enlarged tonsils or adenoids, decreased oral cavity due to low palate, deficiency of maxilla or mandible.

Clinical features

- The degree of macroglossia may be mild to severe.
- Infants may manifest noisy breathing, drooling of saliva, difficulty in eating and lispy speech.
- The enlarged tongue may exert pressure against mandible and teeth, which may produce crenated lateral borders of tongue.
- Sometimes, open bite, mandibular prognathism and ulcerations are seen.
- Airway obstruction may be seen among severe cases.

- *Beckwith–Wiedemann syndrome*
 - Visceromegaly
 - Gigantism
 - Neonatal hypoglycaemia
 - Macroglossia
 - Facial features: Naevus of forehead and eyelids, linear indentations of the ear lobes, maxillary hypoplasia and autosomal dominant inheritance.
- Hypothyroid macroglossia: Smooth, diffuse and generalized enlargement is seen.
- Amyloidosis, neurofibromatosis and MEN IIB syndrome produce nodular type of enlargement.
- Lymphangiomas: Tongue surface shows blebbing with multiple vesicle-like blebs.
- Down's syndrome shows papillary and fissured surface.

Histopathology

Histopathology depends on the following causes:

- Down's syndrome and edentulous patients show normal features.
- Amyloidosis shows abnormal protein deposition.
- Tumours show abnormal proliferation.
- Beckwith–Wiedemann syndrome shows muscular enlargement.

Prognosis and predictive factors

- *Mild cases:* No surgery, speech therapy is given, if speech is impaired.
- *Severe cases:* Partial glossectomy may be needed.

Ankyloglossia

(Synonym: Tongue tie)

It is a developmental anomaly characterized by short, thick lingual frenum resulting in restriction of tongue movement.

Classification

- *Complete ankyloglossia:* Fusion between tongue and floor of the mouth.
- *Partial ankyloglossia:* Tongue tie—short lingual frenum attached to the tip of the tongue.

Clinical features

- **Age.** Neonates.
- **Sex.** Male predilection.
- **Signs and symptoms**
 - Speech difficulties occur due to restricted tongue movement.
 - High mucogingival attachment causes periodontal problems.
 - Ankyloglossia associated with upward and forward displacement of epiglottis results in dyspnoea.
 - *Superior syndrome (glossopalatine ankylosis):* It is a rare condition with congenital adherence of tongue to the palate.

Prognosis and predictive factors

- In children, mostly it is self-corrective.
- If functional and periodontal problems develop, frenectomy is required to allow free tongue movement.

Cleft tongue

- It is due to the lack of merging of lateral lingual swellings.
- It is seen as a deep groove in the midline of the dorsal aspect of the tongue.
- Food debris and microorganisms collect at the base of the cleft and cause irritation.
- It is associated with *oral-facial-digital syndrome.*

Fissured tongue

(Synonym: Scrotal tongue)

- Grooves of varying depths are seen on the dorsal and lateral aspects of the tongue.
- It is seen in *Down's syndrome* and *Melkersson–Rosenthal syndrome* (it is a triad of cheilitis granulomatosa, facial nerve palsy and fissured tongue).
- Debris can get entrapped in the deep grooves.
- These grooves can get interconnected, thus separating the dorsum surface into lobules.
- Histopathologic features include increase in the thickness of lamina propria, loss of filiform papillae of the surface mucosa, hyperplasia of rete pegs, neutrophilic abscess within the epithelium and mixed inflammatory infiltrate.

- ***Treatment:*** No definitive therapy or medication is required. Patient is advised to brush the tongue, as food debris get entrapped in the grooves and can be a source of irritation.

Median rhomboid glossitis

- Initially, it was thought to be a congenital disorder of tongue due to the persistence of tuberculum impar leaving a rhomboid-shaped smooth erythematous mucosa.
- It lacks papilla and taste buds.
- In the recent concept, it is a form of chronic atrophic candidiasis and the condition is now termed as *posterior midline atropic candidiasis.*
- Usually it is seen anterior to circumvallate papilla.
- This lesion is biopsied, if confused with precancerous lesion like erythroplakia.
- It is also called *kissing lesion* because midline soft palate erythema is seen in the areas of routine contact with underlying tongue.
- ***Treatment:*** Antifungal therapy is given to reduce the signs of erythema and inflammation.

Benign migratory glossitis

(Synonym: Geographic tongue)

- It is a smooth depapillated area with serpiginous surrounding and white line, which shows changing pattern on dorsum of tongue.
- The area of desquamation remains for a short time in one location, heals and reappears in another location; therefore, it is also called as *wandering rash.*
- It is also known as *geographic tongue*, since the lesion appears as geographical map on the globe.
- This condition is commonly seen in patients with stress.
- ***Treatment:*** Reassure the patient that it is a benign condition. Burning sensations, if present apply topical steroids and provide zinc supplements. If secondary candidal infection suspected, topical or systemic antifungal medication can be tried.

Hairy tongue

(Synonyms: Lingua nigra; lingua villosa)

- It appears due to defective desquamation of filiform papilla as a result of

which there is hypertrophy of filiform papilla.

- The colour may vary from white to yellow to brown, depending on the type of food and various medicines taken.
- It is seen in people who eat soft diet without including roughage.
- It is also commonly seen in HIV-positive patients.
- It can produce tickling or gagging sensation.
- If there is candidal overgrowth, it will lead to glossopyrosis (burning tongue).
- If there is retention of debris, it will lead to oral halitosis.
- ***Treatment:*** The use of a tongue scraper or surgical dissections of papilla by carbon dioxide laser is advised.

Developmental anomalies of oral lymphoid tissue

Reactive lymphoid aggregate

(Synonym: Reactive lymphoid hyperplasia)

- The lingual tonsil, largest of oral lymphoid aggregate, frequently becomes inflamed and enlarged so that it is clinically evident.
- It is usually bilateral; if evident unilaterally, then it is usually mistaken for early cancer.
- This reactive lingual tonsil is called *foliate papillitis*, referring to vestigial foliate papilla in this area.
- Clinically, it is seen as a firm nodular submucosal mass which may be tender on palpation.
- Since the lymphoid tissue may be the origin of malignant lymphoma, early microscopic diagnosis is essential.

Lymphoid hamartoma

(Synonyms: Castleman tumour; giant benign lymphoma)

- It is a rare disorder characterized by noncancerous benign growths that may develop in the lymph node tissue throughout the body.
- Most often, these occur in the chest, stomach and/or neck.
- Two main types: *Hyaline vascular type* and *plasma cell type*.
 - The *hyaline vascular type* usually presents no symptoms, sometimes develops into noncancerous growth.
 - *Plasma cell type* may be associated with fever, weight loss, skin rash, early destruction of red blood cells and hypergammaglobulinaemia.

Angiolymphoid hyperplasia with eosinophilia

(Synonyms: Epithelioid haemangioma; popular angioplasia)

- Angiolymphoid hyperplasia with eosinophilia (ALHE) is a rare condition that presents with isolated or grouped plaques or nodules in the skin of head and neck.
- It is marked by proliferation of blood vessels with distinctive large endothelial cells, and is accompanied by a characteristic inflammatory infiltrate that includes eosinophils.
- It is benign but persistent and difficult to eradicate.

Pathogenesis

- It is an idiopathic condition, but reactive cause is attributed in most of the cases.
- It also occurs following various forms of trauma or infection.
- The distinctive inflammatory infiltrate in ALHE appears to be intrinsic (not secondary) component of lesion.

Clinical features

- **Age.** 30–33 years.
- **Gender.** Female predilection.
- **Signs and symptoms**
 - It appears as dome-shaped smooth surfaced papules or nodules most often occurring on or near the ear.
 - The colour can range from erythematous to brownish, which may be eroded or crusted, while remaining patients usually demonstrate grouped papules or nodules in a single region.
 - It may be associated with pain or pruritus, rarely pulsations and spontaneous bleeding may occur.

Histopathology

- Biopsy is a must to establish the diagnosis.
- The characteristic histologic features include proliferating capillaries lined by enlarged endothelial cells showing uniform ovoid nuclei and intracytoplasmic vacuoles. These distinctive endothelial features are described as *cobblestone appearance*.
- A perivascular and interstitial lymphocyte and eosinophil infiltrate are seen.
- Lymphoid aggregate with or without follicles is seen.

Prognosis and predictive factors

- Intralesional corticosteroids and irradiation may be employed.
- Surgical removal of lesion may give best result even then the lesion may recur.

Lymphoepithelial cyst

- It develops within a benign lymphoid aggregate or accessory tonsil or oral or pharyngeal mucosa.

- The surface of these may be indented with tonsillar crypts, which might become obstructed by keratin and other debris, or sometimes the opening may be constricted during inflammatory hyperplastic responses.
- *Branchial cleft cyst,* similar but larger cervical lymphoepithelial cyst most probably develops from entrapped salivary duct epithelium in the lymph nodes of the lateral neck.
- *Parotid cyst* is seen in major salivary glands, especially in AIDS patients, but it often lacks a surrounding lymphoid aggregate.

Clinical features

- It presents as yellow or yellow-white discolouration; occasional cysts are transparent.
- Half of the lesions are intraoral lesions that occur on the floor of the mouth; other sites include lateral and ventral surfaces of the tongue, soft palate.
- Occasionally, the superficial cysts rupture and release foul-tasting cheesy, keratinaceous material.

Histopathology

- It is lined by atrophic and often degenerated stratified squamous epithelium, usually lacking rete ridges with minimal granular layer.
- The surface orthokeratin sloughs off and often completely fills the lumen in which sometimes dystrophic calcification can be seen.
- Occasionally, cyst will demonstrate a lining epithelium communicated with well-demarcated aggregate of mature lymphocytes.

Prognosis and predictive factors

- No treatment is necessary unless it is constantly traumatized.
- Most of the lesions are removed by conservative surgical excision to arrive definitive diagnosis.
- It has no malignant potential.

Developmental disturbances of salivary glands

Aplasia of salivary glands

(Synonym: Agenesis)

- Any one or group of salivary glands may be absent, unilaterally or bilaterally.
- It occurs for unknown reasons in isolated cases or in conjunction with other developmental defects such as hemifacial microsomia, the lacrimo-auriculo-dento-digital (LADD) syndrome and mandibulo facialdystosis.
- It usually manifests with the development of xerostomia and its sequelae like burning sensation, oral infections, taste aberrations and difficulty with denture retention.
- ***Diagnosis:*** It is made after exclusion of common causes of dry mouth (medication, Sjögren's syndrome and radiation).

The absence of duct orifice/papilla is an additional clue to scintiscanning.

Hyperplasia of palatal glands

- It is an unusual localized hyperplasia or hypertrophy of minor accessory salivary glands in the palate.
- The cause of this focal enlargement is unknown, although the following factors have been attributed: endocrine disorders, gout, diabetes mellitus, menopause, hepatic cause, starvation, alcoholism, inflammation, autoimmune disorders of salivary gland, ageing process and certain drugs.
- ***Clinical features:*** It presents as a small localized swelling on the hard palate or at the junction of a hard and soft palate, usually asymptomatic, measuring several millimetres to 1 or more centimetres. The lesion has an intact surface and is firm, sessile and normal in colour.
- ***Histopathology:*** Normal appearing mucous acini and ducts are seen without inflammation, spillage of mucin and fibrosis.
- ***Treatment:*** These can be excised for microscopic examination for confirmation.

Atresia

- It is a congenital occlusion or absence of one or more major salivary gland

ducts.

- It is a very rare condition. It may result in the formation of mucous retention cyst and produce severe xerostomia.

Developmental lingual mandibular salivary gland depression

(Synonyms: Static bone cavity; defect of the mandible; latent bone cyst)

- It is an unusual form of slightly aberrant salivary gland where it is found within or adjacent to lingual surface of the body of the mandible in deep and well-circumscribed depression.
- It is more commonly seen in males than in females.
- Radiographically, the lesion appears between the inferior alveolar canal and inferior border of the mandible in the region of second and third molars.
- *Anterior lingual depression:* It is an asymptomatic poorly circumscribed radiolucent area seen in the anterior segment of the mandible between central incisors and premolars.
- This represents anatomic variant related to digastric or sublingual fossa or a developmental anomaly caused by impingement of sublingual gland.
- ***Complications:*** A central salivary gland tumour can develop from the salivary gland tissue.
- ***Treatment:*** Not necessary.

Developmental anomalies of lip

Congenital lip pit

- A pit is a small mucosal invagination based on location; it can be commissural lip pit or median lip pit.
- *Commissural lip pit:* It is seen at the corners of the mouth. It can be unilateral or bilateral. Usually these pits are 1–4 mm deep. It is not associated with any syndrome but very often associated with preauricular pits.
- *Median lip pit:* It is also known as *paramedian lip pit*. It is more prominent than commissural pit. It is usually bilateral and is a depth of 1.5 mm. It is associated with *van der Woude syndrome* (cleft lip, cleft palate along with lip pit).

Double lip

- It is a condition where there is excess tissue in the mucosal aspect of lip.
- Most commonly the upper lip is affected.
- It cannot be seen in relaxed state but when the lips are tensed the double lips represent Cupid's bow shape.
- It is associated with *Ascher's syndrome* (acquired double lip, nontoxic thyroid enlargement, blepharochalasis).

Cheilitis glandularis

- It is an inflammatory disorder of the lip.
- There is a progressive enlargement and eversion of lower labial mucosa.
- The lips may be eroded and ulcerative with formation of crusts.
- This condition has a potential to develop actinic cheilitis and squamous cell carcinoma.
- Biopsy of lower lip will show minor salivary glands, which are normal or atrophied along with chronic inflammatory cells.

Cheilitis granulomatosa

- It is a granulomatous inflammatory swelling of the lip.
- It is episodic initially, after recurrent attack, the swelling becomes persistent.
- It is nontender and involves one or both lips.

- In chronic stage, the lips appear cracked and fissured along with reddish brown discolouration and scaling.
- The fissured lip becomes painful and gradually acquires rubbery consistency.
- Regional lymph nodes are enlarged in 50% of the cases.
- *Miescher–Melkersson–Rosenthal syndrome:* Cheilitis granulomatosa with facial palsy and plicated (scrotal) tongue.
- ***Histopathology:*** A peri- and paravascular chronic inflammatory infiltrate of lymphocytes, plasma cells, histiocytes are seen. Focal areas of noncaseating granuloma formation with epithelioid cells and Langhans-type giant cells are seen.
- ***Treatment***
 - Patch test is done to exclude oral antigens.
 - Antigens should be avoided.
 - Intralesional corticosteroid injections, NSAIDs and mast cell stabilizers are given.
 - Surgery and radiation can also be indicated.

Oral melanotic macule

It is a focal area of melanin deposition seen as a response to local chronic conditions (trauma, tobacco smoking), racial background, systemic medications especially chloroquine.

Clinical features

- **Age.** Younger age group.
- **Gender.** Female predilection.
- **Location.** Vermilion border of lip, buccal mucosa, gingiva, palate.
- **Signs and symptoms**
 - A well-demarcated, uniformly tan-brown, asymptomatic, round oval discolouration which is less than 7 mm in diameter.
 - It has an abrupt onset, does not thicken and has same consistency as surrounding mucosa.
 - *Smoker's melanosis:* It is a special case of oral melanosis found on the gingival/buccal mucosa in heavy smokers with or without concomitant superficial white/grey keratosis.
 - Both pigmentation and keratosis disappear after the cessation of habit.
 - *Clinical significance:* Melanotic macule is innocuous but in some cases it might represent an internal malignancy.

Histopathology

- Normal stratified squamous epithelium with abundant melanin deposits within the melanocytes.
- Deposits can be seen within subepithelial layer of stroma *(melanin incontinence)* or within the macrophages *(melanophages).*
- No inflammatory response will be seen usually.

Prognosis and predictive factors

No treatment is required except for aesthetic considerations.

Hereditary intestinal polyposis syndrome

(Synonym: Peutz–Jeghers syndrome)

- It is an autosomal dominant disorder characterized by intestinal hamartomatous polyps in association with mucocutaneous melanocytic macules.
- ***Aetiology:*** It could be due to germline mutation of STK11 located on band 19p13.3.
- ***Clinical features***
 - Repeated bouts of abdominal pain in patients younger than 25 years are evident.
 - Unexplained intestinal bleeding in young patients, menstrual disturbances in females, cutaneous pigmentation of perioral region crossing vermilion border, perinasal and perioral regions.
 - Pigmentation may fade after puberty.
 - Mucous membrane pigmentation primarily seen in buccal mucosa.
 - The principal morbidity comes from the intestinal location of polyps that includes intussusception, abdominal pain and prolapse of colonic polyp.
- ***Histopathology:*** Extensive smooth muscle arborization is seen throughout the polyp with appearance of pseudoinvasion.
- ***Treatment:*** Surgical treatment for cancers.

Orofacial clefts/cleft lip and palate

Orofacial clefts

- A facial cleft results due to the lack of fusion of facial embryonic processes.
- These are cleft lip, cleft palate, the combination of cleft lip and palate, median cleft of upper lip, oblique facial cleft and lateral facial cleft.

Cleft lip and palate

Occurrence of cleft lip and cleft palate: 50% of cases are cleft lip and cleft palate, 20% of isolated cleft lip, and 30% of isolated cleft palate.

Pathogenesis

- Polygenic or multifactorial inheritance.
- Monogenic or syndromic associated with a variety of other congenital anomalies, nutritional disturbances (e.g. riboflavin deficiency), emotional stress, late pregnancy, defective vascular supply, mechanical disturbance like alcohol, drugs and toxins.
- Circulating substances like alcohol, drugs and toxins.
- Infections like German measles.
- Lack of developmental force.

Classification

- **Veau's classification**
 - *Group I:* It is a defect of soft palate alone.
 - *Group II:* It is a defect of hard and soft palate.
 - *Group III:* It is a defect of soft palate extending to alveolus and lip.
 - *Group IV:* Complete bilateral cleft.
- **ICPR (International Conference of Plastic and Reconstructive Surgery) classification**
 - *Group I:* Cleft of lip or alveolus.
 - *Group II:* Cleft of secondary palate.
 - *Group III:* Combined cleft of primary and secondary palates.

Clinical features

- Isolated cleft palate is more common in females.

- Cleft lip/palate is more common in males.
- As cleft palate creates a communication between the oral and nasal cavities, patients often feel difficulty in taking foods and drinks due to nasal regurgitation.
- Breast feeding is very difficult as babies cannot generate sufficient suction.
- In case of cleft palate, maxillary anterior teeth may be misplaced, deformed or impacted.
- Usually retrusion of maxilla with narrow palatal arch is seen.
- Deflection of nasal tip towards the noncleft side and larger naris on the cleft side.
- Bilateral complete cleft shows complete separation of the anterior palate, which projects towards the mid portion of the lip and is attached only by the nasal septum.

Prognosis and predictive factors

- It is a team effort (multidisciplinary approach). The team consists of genetic counsellor, prosthodontist, plastic surgeon, orthodontist, paediatrician and speech therapist.
- Surgical treatment includes primary lip closure, which is done by following the *rule of 10* for the child:
 - 10 pounds of weight
 - 10 weeks of age
 - 10 g/dl of haemoglobin
- Prosthesis should be provided to avoid nasal regurgitation and allow proper feeding of child.

Developmental disturbances of the oral mucosa

Fordyce's granules

- These are ectopic sebaceous glands that occur on buccal mucosa.
- These are normal anatomic variants.
- These are seen as multiple yellow or yellowish white papillar lesions.
- ***Location:*** Buccal mucosa, lateral border of the vermilion portion of upper lip.
- These are few to hundreds in number.
- Lesions are asymptomatic and give a feeling of roughness to the mucosa.
- ***Histopathology:*** These closely resemble normal sebaceous gland found in the skin. The acinar lobules are seen beneath the epithelial surface, and they communicate with the outer surface via a central duct. The acini in the lobule are polygonal in shape with a centrally located nuclei and abundant cytoplasm. There will be no associated hair follicle.
- ***Treatment:*** No treatment required.

Leukoedema

- It is a diffused greyish to white, milky opalescent appearance of buccal mucosa.
- The lesion cannot be rubbed off but the whitish appearance greatly reduces when the cheeks are stretched.
- It is typically seen among smokers.
- ***Location:*** It occurs bilaterally on the buccal mucosa and extends on to the labial mucosa.
- ***Histopathology***
 - Increased thickness of epithelium is seen.
 - Usually epithelium will be parakeratinized.
 - There is intracellular oedema in the spinous cell layer which is termed as *spongiosis*.

Focal epithelial hyperplasia

(Synonym: Heck's disease)

- It is one of the most contagious of the HPV-induced oral papillary lesions.
- It can be produced by any of the subtypes of HPV-13 to HPV-32.

- **Clinical features**
 - It primarily occurs among children.
 - It is usually seen on labial, buccal and lingual mucosa.
 - It appears as broad-based or slightly elevated well-demarcated plaques or flat topped lesions.
 - It may be pale or rarely white in colour.
 - Sometimes hyperplastic lesions are small, discrete and well-demarcated, but they frequently cluster so loosely together that the entire mucosal area takes on a cobblestone or fissured appearance.
- ***Histopathology:*** It shows extreme hyperplasia or acanthosis of spinous cell layer with minimum production of surface projections and/or induction of connective tissue proliferation.
- ***Treatment:*** Conservative surgical excision.

Developmental disturbances of gingiva

Fibromatosis gingiva

(Synonyms: Elephantiasis gingival fibromatosis; hereditary gingival fibromatosis)

- It is a diffuse fibrous overgrowth of gingival tissue.
- It is transmitted through autosomal dominant gene.
- There is smooth or nodular overgrowth of the gingival tissue affecting one or both the arches.
- Usually it is seen at the time of eruption of permanent incisors.
- The tissue is normal or pale in colour.
- If the tissue is too firm, it can prevent the normal eruption.
- This condition is not painful and there is no tendency for haemorrhage.
- ***Histopathology:*** The epithelium is thickened and the connective tissue is composed of thick collagen bundles along with few blood vessels.
- ***Treatment:*** Surgical removal of this tissue is done to expose the teeth.

Developmental disturbances of jaws

Agnathia

(Synonyms: Otocephaly; holoprosencephaly)

- It is an absence of maxilla or mandible.
- It is partial or total absence of jaw.
- In maxilla, one maxillary process or premaxilla will be missing.
- In mandible, it is more common to find a portion of mandible missing, more commonly condyle or ramus is found to be missing.
- It is a very rare condition.

Micrognathia

- It is a small jaw involving either maxilla or mandible.
- It can be divided into true and relative conditions.
 - *True micrognathia:* It can be congenital or acquired.
 - *Congenital:* Example: Pierre Robin syndrome.
 - *Acquired:* Example: Due to infection of TMJ, ankylosis of TMJ and agenesis of condyle.
 - *Relative micrognathia:* It is due to the abnormal relation of one jaw to the other or jaw to the skull which gives illusion of micrognathia.
- ***Radiographic features:*** Deficiency of premaxillary areas, posterior positioning of mandible, severe retrusion of chin and agenesis of condyle.

Macrognathia

- It refers to large jaw.
- It can be either true or relative macrognathia.
- Macrognathia is seen in conditions like pituitary gigantism, Paget's disease and fibrous dysplasia.
- ***Clinical features:*** Include long ramus, excessive condylar growth and mandibular prognathism.

Facial hemihypertrophy

- It is a developmental anomaly which proceeds in asymmetric overgrowth of one or more body parts.
- It may be associated with syndrome like *Beckwith–Wiedemann syndrome.*
- ***Clinical features***

- Females are more commonly affected.
- In buccal mucosa, it appears velvety and hangs in soft pendulous folds on the affected side.
- Tongue shows unilateral macroglossia and contralateral displacement.
- Premature shedding and eruption of teeth is seen on the affected side.
- Alveolar bone of the maxilla and mandible is enlarged, wider and thicker, sometimes altered trabecular pattern is seen.

- ***Treatment:*** No specific treatment is done except for cosmetic reasons.

Facial hemiatrophy

(Synonym: Parry–Romberg syndrome)

- Slowly progressive atrophy of soft tissue along with wasting of fat, muscles and bones is seen.
- The changes are confined to one-half of the face.
- Contralateral epilepsy, trigeminal neuralgia and changes in the eye and hair are seen.
- It may be a form of localized scleroderma.
- It is seen commonly among females.
- Initially, while line or furrow (coup-de-sabre) and later, a painless cleft is seen in the midline of forehead.
- Pigmented lesions are seen either in midline or close to the corner of mouth.
- Oral manifestations include incomplete root formation, delayed eruption, atrophy of lip and tongue, reduced growth of maxilla and tongue.

Developmental disturbances affecting number of teeth

Anodontia

(Synonym: Anodontia vera)

- Anodontia is the congenital absence of all teeth (partial anodontia or hypodontia), involving both the dentitions or only teeth of the permanent dentition.
- There is lack of tooth development due to true failure of odontogenesis.
- It may be associated with *ectodermal dysplasia.*
- Anodontia is usually part of a syndrome and seldom occurs as an isolated entity.
- The anodontia may contribute to masticatory dysfunction, speech impairment, aesthetic problems and malocclusion.
- Absence of lateral incisors represents a major stereotype.
- Congenital absence of all wisdom teeth, or third molars, is relatively common.
- ***Classification***
 - *True anodontia*
 - *Total anodontia:* Example: Ectodermal dysplasia.
 - *Partial anodontia:* Example: In permanent dentition, third molar, maxillary lateral incisors, maxillary or mandibular second premolars and in deciduous dentition, maxillary lateral incisors and mandibular cuspids.
 - *Pseudo-anodontia:* It is due to multiple unerupted teeth.
 - *False (induced) anodontia:* It is due to extraction of teeth.

Hypodontia

- Partial anodontia is known as*hypodontia* or *oligodontia.*
- It is the condition in which the patient has missing teeth as a result of their failure to develop.
- Hypodontia describes a condition where the patient has missing up to six teeth, excluding the third molars.
- The condition of missing over six teeth, excluding third molars or wisdom teeth, is called *oligodontia*.
- The most common missing teeth are the wisdom teeth (25–35%), the

upper lateral incisors (2%), the lower second premolar (3%) or the upper second premolar, with a female predilection.
- In primary dentition, the maxilla is more affected, with the condition usually involving the maxillary lateral incisor.

Pathogenesis

- The cause of isolated missing teeth remains unclear, but the condition is believed to be associated with genetic, hormonal, environmental and infectious factors during dental development.
- Hypodontia is often familial and can also be associated with genetic disorders such as ectodermal dysplasia or Down's syndrome.
- Hypodontia can also be seen in people with cleft lip and palate.
- ***Aetiology:*** Due to hormonal defects, includes idiopathic hypoparathyroidism and pseudohypoparathyroidism.
- Environmental causes involve exposure to radiation, anticancer chemotherapeutic agents, allergy and toxic epidermal necrolysis after drug administration.
- Infectious causes of hypodontia include rubeolla and candidiasis *(candida endocrinopathy syndrome).*
- Genetic causes also involve the genes *MSX1*and *PAX9*.

Hyperdontia

(Synonym: Supernumerary teeth)

- The presence of any extra tooth or teeth in the dental arch, in addition to the normal series of teeth, is known as *supernumerary teeth*.
- It is suggested that supernumerary teeth develop from a second tooth bud arising from the dental lamina near the regular tooth bud or possibly from splitting the regular tooth bud itself.
- Supernumerary teeth in deciduous teeth are less common than in permanent teeth.
- *Hyperdontia in permanent dentition:* The common sites are maxillary incisor region—*mesiodens*, maxillary fourth molar, mandibular fourth molar, maxillary lateral incisor followed by maxillary and mandibular cuspids. *Paramolar* is an additional molar, either buccal or lingual to the existing molar. *Distomolar* or *distodens* is an additional molar located distal to the existing molar.
- In deciduous dentition, maxillary lateral incisors and maxillary or mandibular cuspids are the most common sites for supernumerary teeth.

- Hyperdontia is seen in various disorders including Gardner's syndrome, cleidocranial dysostosis, cleft lip and palate.
- **Morphological classification of supernumerary teeth**
 - *Conical teeth*: Example: Mesiodens.
 - *Tuberculate:* Example: Teeth possessing more than one cusp or tubercle found on the palatal aspect of central incisors.
 - *Supplemental*: A condition where there is duplication of teeth in the normal series. Example: Permanent maxillary lateral incisors.
 - *Odontome*: It is an odontogenic tumour.

Gardner's Syndrome

Multiple polyposis of the large intestine.
Osteomas of the bones including long bones, skull and jaws.
Multiple epidermoid or sebaceous cysts of the skin.
Desmoid tumours.
Impacted supernumerary and permanent teeth.

Developmental disturbances affecting the size of teeth

Microdontia

- It is a condition in which the teeth appear smaller than normal.
- In the generalized form, all teeth are involved.
- In the localized form, only a few teeth are involved.
- The most common teeth affected are the upper lateral incisors and third molars.
- The affected teeth may be of normal or abnormal morphology.
- There are three types of microdontia:
 1. True generalized microdontia
 2. Relative generalized microdontia
 3. Microdontia involving a single tooth
- *True generalized microdontia*
 - All the teeth are smaller in size, mainly reported in the case of pituitary dwarfism.
 - All the teeth are well formed and small.
- *Relative generalized microdontia*
 - There is an illusion of true microdontia.
 - Normal teeth are seen in large-sized jaws.
- *Microdontia involving a single tooth*
 - It commonly affects the maxilla, mainly lateral incisors or third molar.
 - Usually lateral incisors become peg shaped.

Macrodontia

(Synonyms: Megadontia; megalodontia)

- It is a condition in which any tooth or teeth appear larger than normal for that particular type of tooth.
- True macrodontia that involves the entire dentition is rare.
- It is more common that there is an enlargement of a single tooth due to a disturbance of morphodifferentiation.
- It should not be confused with taurodontism (bull teeth), fusion (double tooth) or the jaws being relatively small, giving the appearance of macrodontia.
- It is classified as:

1. True generalized macrodontia
2. Relative generalized macrodontia
3. Macrodontia of single teeth

- *True generalized macrodontia* is usually attributed to a hormonal imbalance and pituitary gigantism.
- *Relative generalized macrodontia* includes large-sized tooth present in a small-sized jaw.
- The cause for *single tooth macrodontia* is unknown.

Developmental disturbances affecting shape of teeth

Tooth fusion (fig. 1.5)

- It arises through union of two normally separated tooth germs and depending upon the stage of development of the teeth at the time of union, it may be either complete or incomplete.
- If the contact occurs before calcification, the two teeth will be completely united to form a single large tooth. If the tooth crown is completed, the dentine is always confluent. The tooth count reveals a missing tooth when the anomalous tooth is counted as one.
- Usually, two independent pulp chambers and root canals can be seen. However, fusion can also be the union of a normal tooth bud to a supernumerary tooth germ. In these cases, the number of teeth is fewer, if the anomalous tooth is counted as one tooth.
- ***Clinical significance:*** Appearance, spacing and periodontal problems.

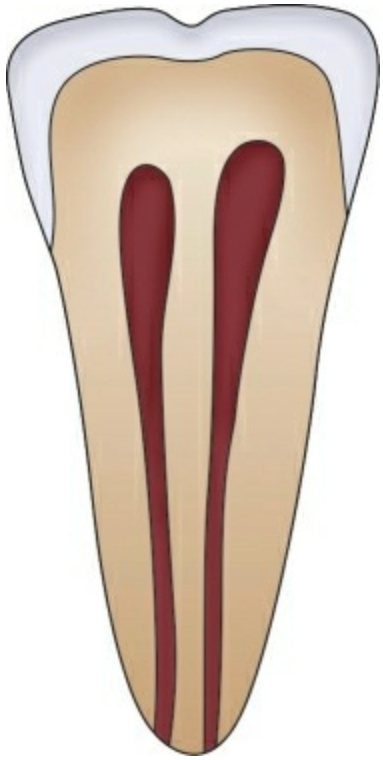


FIG. 1.5 Tooth fusion.

Gemination (fig. 1.6)

- It arises when two teeth develop from one tooth bud and as a result the patient has an extra tooth, in contrast to fusion, where the patient would appear to have extra tooth.
- In geminated teeth, division is usually incomplete and results in a large tooth crown that has a single root and a single canal.
- Both gemination and fusion are prevalent in primary dentition, with incisors being more affected.
- *Twining:* It is the division of tooth bud into equal structures resulting in one normal and another supernumerary tooth.

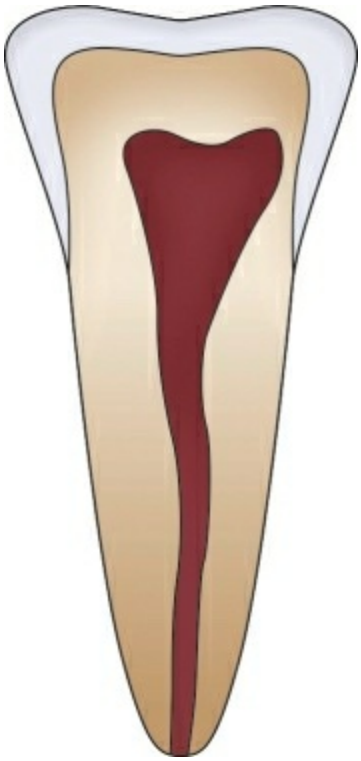


FIG. 1.6 Gemination.

Concrescence (fig. 1.7)

- It is a condition of teeth where the cementum overlying the roots of at least two teeth join together. The cause can sometimes be attributed to trauma or crowding of teeth.
- ***Clinical significance:*** Surgical separation of the teeth may be necessary, if one is to be extracted.

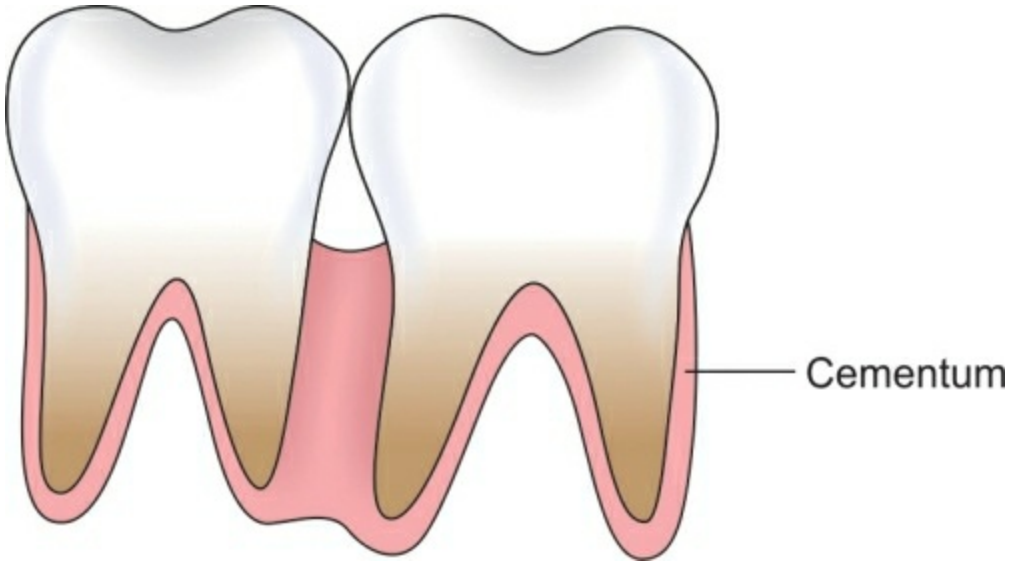


FIG. 1.7 Concrescence.

Dens evaginatus (fig. 1.8)

(Synonyms: Occlusal enamel pearl; Leong's premolar; occlusal tuberculated premolar; evaginated odontome)

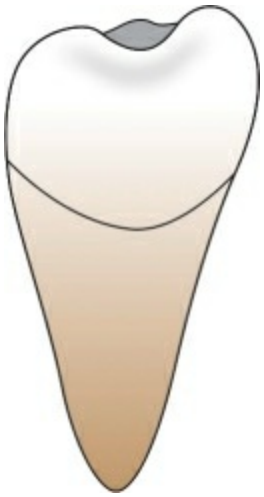


FIG. 1.8 Dens evaginatus.

- It is a condition found in teeth where the outer surface appears to form an extra cusp.
- It may occur due to the proliferation and evagination of inner enamel epithelium along with underlying odontogenic mesenchyme. This can cause incomplete eruption or pulpal exposure on occlusal wear.

- Premolars are more likely to be affected than any other tooth.
- Dens evaginatus may be seen more frequently in Down's syndrome patients.
- It may be bilateral and mainly seen in mandibular arch. This accessory cusp contains enamel, dentine and pulp.
- ***Clinical significance:*** The pulp of the tooth may extend into the dens evaginatus. There is a risk of the dens evaginatus chipping off in normal function; hence this condition requires monitoring as the tooth can lose its blood and nerve supply as a result and may need root canal treatment.

Dens invaginatus

(Synonyms: Dens in dente; dilated composite odontome)

- Dens invaginatus is a deep surface invagination of the crown or root that is lined by enamel.
- It occurs in two forms:
 - Coronal dens invaginatus
 - Radicular dens invaginatus
- **Coronal dens invaginatus** (Fig. 1.9a)
 - It is seen more frequently.
 - In order of decreasing frequency, the teeth affected most often include the permanent lateral incisors, central incisors, premolars, canines and molars.
 - It has been classified into three major types:
 1. Type I exhibits an invagination that is confined to the crown.
 2. Type II exhibits an invagination that extends below the cemento enamel junction and ends in a blind sac that may or may not communicate with the adjacent dental pulp.
 3. Type III exhibits an invagination that extends through the root and perforates in the apical or lateral radicular area without any immediate communication with the pulp.

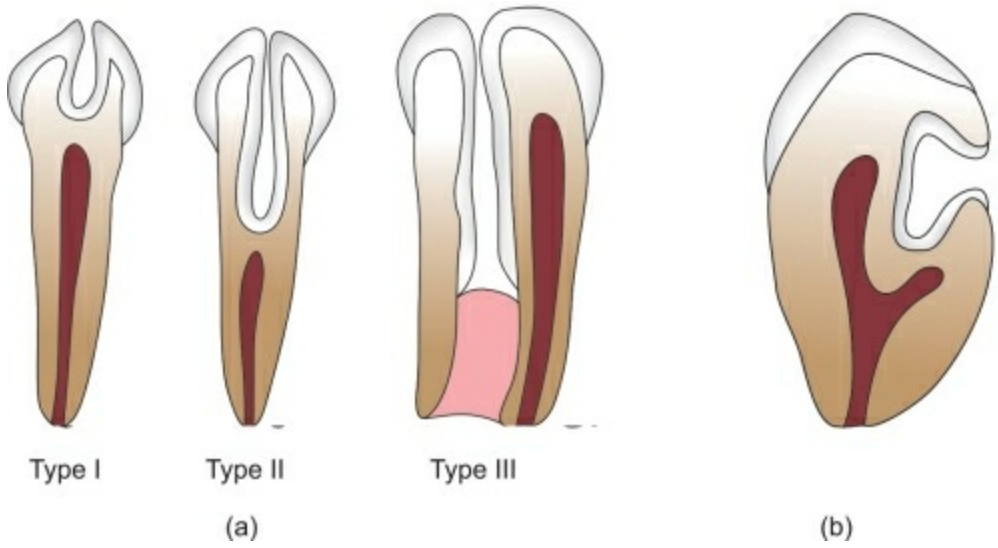


FIG. 1.9 (a) Coronal dens invaginatus. (b) Radicular dens invaginatus.

Note: Occasionally, the invagination may be large and resemble a tooth with a tooth, hence the term *dens in dente*.

In some cases the invagination may be dilated and disturb the formation of the tooth, resulting in anomalous tooth development termed *dilated odontome*.

- **Radicular dens invaginatus** (Fig. 1.9b): It is rare and thought to arise secondary to a proliferation of Hertwig's root sheath, with the formation of a strip of enamel that extends along the surface of the root.
- ***Clinical significance:*** Debris can get collected and tooth gets infected by caries.
- Root canal therapy may present severe problems because of the complex anatomy of the teeth.

Dilaceration (fig. 1.10)

- It refers to an *angulation* or a sharp bend or curve in the root or crown of a formed tooth.
- The condition is thought to be due to trauma during the period in which tooth is forming. The result is that the position of the calcified portion of the tooth is changed and the remainder of the tooth is formed at an angle. Such an injury to a permanent tooth, resulting in dilaceration, often

follows traumatic injury to the deciduous predecessor in which that tooth is driven apically into the jaw.

- The curve or bend may occur anywhere along the length of the tooth, sometimes at the cervical portion, at other times midway along the root or even just at the apex of the root, depending upon the amount of root formed when the injury is occurred.
- ***Clinical significance:*** Difficulty to encounter extraction.

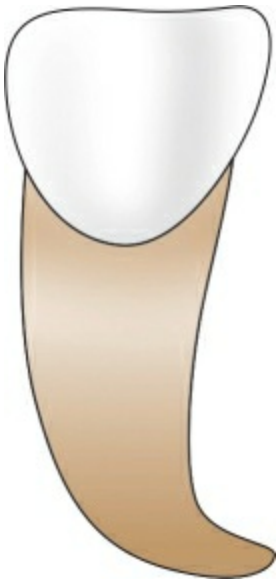


FIG. 1.10 Dilaceration.

Accessory cusps

Talon cusp

- It is an anomalous structure resembling an eagle's talon, projects lingually from the cingulum area of a maxillary or mandibular permanent incisor.
- This cusp blends smoothly with the tooth except that there is a deep developmental groove where the cusp blends with the sloping lingual tooth surface.
- It is composed of normal enamel, dentine and a horn of pulp tissue.
- It is commonly associated with Rubinstein–Taybi syndrome (developmental retardation, broad thumbs and great toes, characteristic facial features, delayed or incomplete descent of testes in males and short stature).

- ***Clinical significance:*** Appearance, caries control, occlusal accommodation, pulpal exposure requiring endodontic treatment.

Cusp of carabelli

- Accessory cusp is located on the palatal surface of mesiolingual cusp of maxillary first molar.
- A similar cusp seen in mandibular molar on the buccal aspect of mesiobuccal cusp is called *protostylid*.

Dens invaginatus: Already discussed on page 19.

Taurodontism

- It is a condition whereby the body of the tooth and pulp chamber is enlarged vertically at the expense of the roots. As a result, the floor of the pulp and the furcation of the tooth are moved apically down the root.
- The underlying mechanism of taurodontism is the failure or late invagination of Hertwig's epithelial root sheath, which is responsible for root formation and shaping causing an apical shift of the root furcation. The constriction at the cementoenamel junction is usually reduced or absent.
- An enlarged pulp chamber, apical displacement of the pulpal floor and no constriction at the level of the cementoenamel junction are the characteristic features.
- Taurodontism is most commonly found in permanent dentition although the term is traditionally applied to molar teeth.
- In some cases, taurodontism seems to follow an autosomal dominant type of inheritance.
- Taurodontism is found in association with *amelogenesis imperfecta, ectodermal dysplasia, mesiobuccal cusp and tricho-dento-osseous syndrome.*
- The term *bull-like teeth* is derived from similarity of these teeth to those of ungulate or cud-chewing animals.
- According to Shaw, it can be classified as *hypotaurodont, hypertaurodont* and *mesotaurodont* (Fig. 1.11).
- According to Mangion, taurodontism may occur due to:
 - Retrograde character
 - Primitive pattern
 - Mendelian recessive character
 - Atavistic feature
 - Mutation

- The condition is of anthropological importance as it was seen in Neanderthals.
- The teeth involved are invariably molars; sometimes single and sometimes multiple teeth may be involved. The teeth themselves may look normal and do not have any particular anatomical character on clinical examination.
- On a dental radiograph, the involved tooth looks rectangular in shape without apical taper. The pulp chamber is extremely large and the furcations may be only a few millimetres long at times.
- Increased number of roots present more than as described in the normal dental anatomy.
- The teeth involved are third molars, mandibular cuspids and bicuspids.
- *Clinical significance:* Direction of accessory root canal needs to be verified during endodontic treatment.

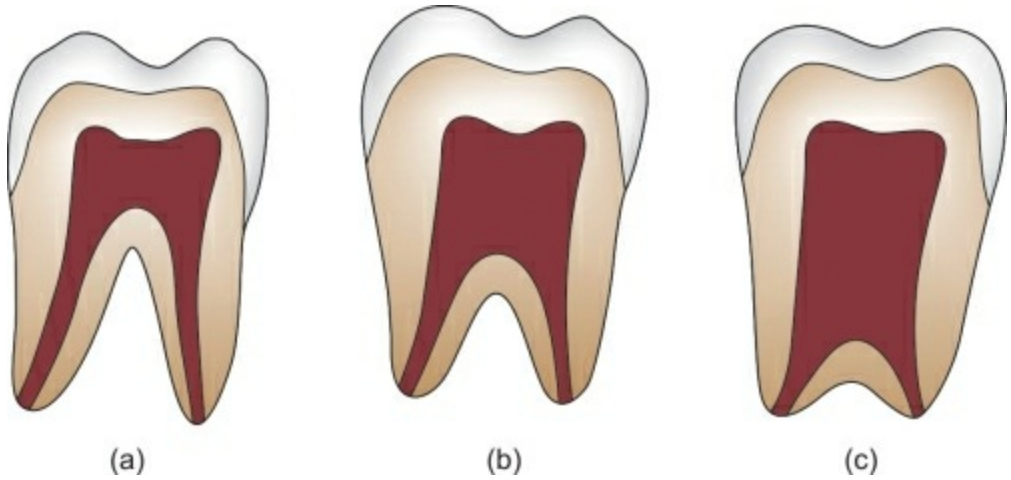


FIG. 1.11 Classification of taurodontism: (a) Hypotaurodont; (b) mesiotaurodont; (c) hypertaurodont.

Developmental disturbances affecting the eruption pattern of dentition

Premature eruption

- *Natal teeth:* These are deciduous teeth that have erupted prematurely into the oral cavity at the time of birth in infants.
- *Neonatal teeth:* These are deciduous teeth that erupt prematurely into the oral cavity within first 30 days after birth. Mandibular central incisors are commonly seen.
- Premature shedding of deciduous teeth also leads to premature eruption of permanent teeth.

Delayed eruption

- It is seen in both deciduous and permanent dentitions.
- Systemic factors causing delayed eruption include rickets, cretinism, cleidocranial dysplasia and fibromatosis gingiva.
- Delayed eruption in permanent dentition: Retained deciduous teeth, impaction, ankylosis, certain cysts or tumours and endocranial disturbances.

Embedded teeth

These are teeth that are not erupted because of lack of eruptive forces. There is no other associated aetiology.

Impacted teeth

- These teeth are not erupted due to some barrier in the path of eruption, even though eruptive forces may be present.
- Aetiologies of impacted tooth are due to
 - Lack of space in the dental arch
 - Some form of trauma during development
 - Thick overlying soft tissue
 - Cysts and tumours
 - Rotation of tooth buds
 - Endocranial disturbances
- The most common impacted teeth in permanent dentition are the mandibular third molar, maxillary third molar and maxillary canine.

- In deciduous dentition, mandibular second molars are most commonly impacted.
- ***Classification***
 1. *Winter's classification,* depending on the long axis of tooth
 Mesioangular deflected
 Distoangular deflected
 Vertical deflected
 Horizontal deflected
 Buccal deflected
 Lingual deflected
 2. *Complete (full/bony) or incomplete (partial) impaction*, depending on whether the tooth is completely surrounded by the bone or partially by the soft tissue and partially in bone.
- ***Complications***
 - It can cause resorption of adjacent teeth.
 - Pain and trismus.
 - Dentigerous cyst can be developed.
- ***Treatment***
 - Molars are surgically removed.
 - Canines are brought into occlusion orthodontically.

Ankylosed deciduous teeth

(Synonym: Submerged tooth)

- This condition is produced due to absence of periodontal ligament and subsequent fusion of teeth to the alveolar bone.
- Deciduous second molars are most frequently ankylosed to alveolar bone; soon there will be an increase in the height of jaw bone and the permanent first molar will erupt behind the deciduous molar, and in comparison the second deciduous molar will be at a lower occlusal level thus appearing submerged.
- On percussion, it produces a solid sound instead of a dull cushion sound.
- Radiographically, partial absence of periodontal ligament blends with tooth root and bone.
- ***Treatment:*** Surgical removal, to prevent development of malocclusion, local periodontal diseases and dental caries.

Developmental disturbances affecting structure of teeth

Amelogenesis imperfecta

(Synonyms: Hereditary brown opalescent teeth; hereditary enamel dysplasia; hereditary brown teeth)

Definition

- It is a group of hereditary defect unassociated with any other generalized defect or systemic disorder. It is entirely an ectodermal disorder.
- Amelogenesis imperfecta can be of three types:
 1. *Hypoplastic:* Defective matrix formation
 2. *Hypocalcified:* Defective mineralization of matrix
 3. *Hypomaturation*: Enamel fails to mature
- Genetic study reveals an alteration of the gene coding for the protein of enamel, amelogenin and the gene is at the locus DXS 85 and this is present in the chromosome Xp22.

Classification (Witkop, 1989)

- **Type I: Hypoplastic**
 - **IA:** Hypoplastic, pitted autosomal dominant
 - **IB:** Hypoplastic, local autosomal dominant
 - **IC:** Hypoplastic, local autosomal recessive
 - **ID:** Hypoplastic, smooth autosomal dominant
 - **IE:** Hypoplastic smooth X-linked dominant
 - **IF:** Hypoplastic rough autosomal dominant
 - **IG:** Enamel agenesis, autosomal recessive
- **Type II: Hypomaturation**
 - **IIA:** Hypomaturation, pigmented autosomal recessive
 - **IIB:** Hypomaturation, X-linked recessive
 - **IIC:** Snow-capped teeth, autosomal dominant
- **Type III: Hypocalcified**
 - **IIIA:** Hypocalcified, autosomal dominant
 - **IIIB:** Hypocalcified, autosomal recessive
- **Type IV: Hypomaturation—hypoplastic with taurodontism**
 - **IVA:** Hypomaturation—hypoplastic with taurodontism, autosomal

dominant
- **IVB:** Hypoplastic—hypomaturation with taurodontism, autosomal dominant

Clinical features

- **Type I:** In generalized or localized pitted pattern, there are pinpoint pits which undergo staining. The buccal surfaces of teeth are more affected.

In smooth pattern, enamel surface is thin, glossy and without appropriate thickness.

The teeth are shaped like crown preparation. The teeth will be opaque white or translucent brown. In rough pattern, the enamel is denser than the smooth pattern but has rough surface. The teeth are yellow to white in colour.

In enamel agenesis, there is a total lack of enamel formation.

- **Type II:** The teeth are normal in shape but the enamel is much softer.
- **Type III:** The teeth are shaped normally but after a period of function the enamel is lost.

Radiographic features

- The enamel may be completely absent.
- If present, it appears as a thin layer over the cusp tips and interproximal areas.
- If calcification is defective, the radiodensity of enamel becomes the same as that of dentine.

Histopathology

- *Hypoplasia:* Matrix formation is defective.
- *Hypocalcification:* Improper mineralization.
- *Hypomaturation:* Alteration in the enamel rod and sheath structure.

Prognosis and predictive factors

- Improve the cosmetic appearance by full crown or veneer.
- Full denture can be provided in cases of enamel agenesis.

Dentinogenesis imperfecta

(Synonym: Hereditary opalescent teeth)

- It is the hereditary developmental disturbances of dentine.

- The gene affected is present on chromosome 4 and it codes for DSPP (dentine sialoprotein and phosphoprotein).
- Dentine defect associated with opalescent teeth and bone disease is termed as osteogenesis imperfecta with opalescent teeth.

Classification

- **Shield's classification**
 - *Dentinogenesis imperfecta, type 1:* Dentinogenesis imperfecta without osteogenesis imperfecta.
 - *Dentinogenesis imperfecta, type 2:* Dentinogenesis imperfecta with osteogenesis imperfecta.
 - *Dentinogenesis imperfecta, type 3:* This is seen as racial isolate in Maryland and it is called *Brandywine type.*
- Extensive studies have proven that dentinogenesis imperfecta is clearly a disorder from osteogenesis imperfecta hence the following **revised classification** is proposed:
 - *Dentinogenesis imperfecta 1:* Dentinogenesis imperfecta without osteogenesis imperfecta (opalescent dentine): This corresponds to dentinogenesis imperfecta type II of Shield's classification.
 - *Dentinogenesis imperfecta 2: Brandywine type* dentinogenesis imperfecta: This corresponds to dentinogenesis imperfecta type III of Shield's classification.
 - *There is no substitute in the present classification for the category designated as Dentinogenesis imperfecta type I of the Shield's classification.*
- **Dentinogenesis imperfecta 1**
 - The teeth are bluish grey colour or amber brown and opalescent.
 - The enamel separates readily due to occlusal force.
 - *Radiographic features:* The teeth have bulbous crowns with narrow pulp chamber and root canal which may later get obliterated.
- **Dentinogenesis imperfecta 2**
 - The crowns of deciduous and permanent teeth wear rapidly after eruption and multiple pulp exposures may occur.
 - The dentine is amber and smooth.
 - *Radiographic features:* The deciduous dentition shows very large pulp chambers and root canals. The permanent teeth have pulpal spaces that are either smaller than normal or completely obliterated.
 - When teeth show extremely thin dentine covering enlarged pulp, it is called as *shell teeth*.

Histopathology

- **Dentinogenesis imperfecta 1**
 - The enamel appears normal.
 - Dentine is composed of irregular tubules, often with large areas of uncalcified matrix.
 - Dentine may contain fewer number of tubules, which are larger in diameter.
 - In some areas, there is absence of tubules and dentinal matrix remains uncalcified.
 - Cellular inclusions probably odontoblasts in the dentine are not uncommon.
 - The pulp chamber is obliterated due to continuous deposition of dentine.
- **Dentinogenesis imperfecta 2:** Not adequately documented.

Prognosis and predictive factors

- It is directed primarily towards preventing the loss of enamel and subsequent loss of dentine through attrition.
- Crowns can be used for considerable success, although care must be taken in the preparation of the teeth.

Dentine dysplasia

- It is a genetic disorder of teeth, commonly exhibiting an autosomal dominant inheritance.
- It is characterized by the presence of normal enamel but atypical dentine with abnormal pulpal morphology.
- There are two types of dentine dysplasia:
 1. *Type I:* Radicular dentine dysplasia
 2. *Type II:* Coronal dentine dysplasia

Radicular dentine dysplasia (rootless teeth)

- The roots of teeth are shorter than normal as a result of disorganized dentine and the pulp chamber significantly reduced.
- The enamel and coronal dentine is normal.
- The teeth will exhibit extreme mobility.
- ***Radiographic features:*** Roots are short, blunt and conical. In deciduous tooth, the roots are short, the pulp chamber and root canals are

completely obliterated. In permanent dentition, in mild cases, there are pulp stones and periapical radiolucencies, and in moderate to severe cases, these may be crescent shaped.

- ***Histopathology:*** The coronal dentine is normal. In the roots, the normal dentinal tubule formation appears to have blocked, so the new dentine formed in whorls around the obstacles. There are repetitive attempts to form root structure and is circumscribed as *lava flowing around boulder*.

Coronal dentine dysplasia

- The root length is normal in both dentitions. Clinically, the deciduous teeth appear bluish grey to yellowish brown and the permanent teeth appear normal.
- ***Radiographic features:*** The pulp chamber of the deciduous teeth becomes obliterated in deciduous teeth. While in permanent teeth, large pulp chamber is seen in coronal portion of the tooth, which is referred to as *thistle tube appearance.* Pulp stones may be found.
- ***Histopathology:*** The deciduous teeth exhibit amorphous and a tubular dentine in the radicular portion, while coronal dentine is relatively normal. The permanent teeth also show relatively normal coronal dentine, but the pulp has multiple pulp stones.
- ***Prognosis and predictive factors:*** There is no treatment for the disease, and its prognosis depends upon the occurrence of periapical lesions necessitating tooth extraction as well as upon the exfoliation of teeth due to increased mobility.

Regional odontodysplasia

(Synonyms: Odontodysplasia; odontogenesis imperfecta; ghost tooth)
It is an uncommon developmental abnormality of teeth, usually localized to a certain area and nonhereditary.

Pathogenesis

- The exact aetiology is unknown.
- Latent virus, circulatory deficiency, trauma or infection, mutation, medication taken during pregnancy and radiation therapy may play a role for regional odontodysplasia.
- The latent virus may reside in the odontogenic epithelium which subsequently becomes active during tooth development.

Clinical features

- No predilection for race, but females are more likely to be affected by regional odontodysplasia.
- The maxillary anterior teeth are involved more frequently than the mandibular teeth.
- The deciduous teeth as well as the permanent teeth may be involved.
- Usually, teeth fail to erupt and if erupt, they demonstrate yellow to brown irregular crown surfaces.

Radiographic features

- Thin enamel and dentine surrounding radiolucent pulp is seen.
- There is no contrast between the dentine and enamel and the coronal portion appears very indistinct.
- The radiographs are unique characteristics showing a marked reduction in radiodensity so that the teeth assume a *ghost appearance;* hence it is called *ghost teeth*.

Histopathology

- The marked reduction in the amount of dentine, the widening of the predentine layer, the presence of large areas of interglobular dentine and an irregular tubular pattern of dentine are seen.
- Characteristically, the reduced enamel epithelium around nonerupted teeth shows many irregular calcifies bodies.

Prognosis and predictive factors

- Treatment is usually based upon keeping these teeth and preserving the alveolus.
- For erupted teeth, endodontics is an option, if the tooth is devitalized and restorable.
- For unerupted teeth, function can be restored with a removable partial denture until all major growths have been completed, and a final restoration can be placed.

Enamel hypoplasia

Enamel hypoplasia is defined as the incomplete or defective formation of the organic enamel matrix of teeth.

Types of enamel hypoplasia

Two types of enamel hypoplasia exist (Table 1.1):
1. Hereditary
2. Environmental

Table 1.1

Types of enamel hypoplasia

Hereditary	Environmental
Both the dentition can be affected	Either of the dentition can be affected including a single tooth hypoplasia may occur
Only enamel is affected	Enamel and dentine are affected to certain extent or degree

Causes of environmental enamel hypoplasia

Various causes of environmental enamel hypoplasia are:

- Nutritional deficiency (vitamins A, C and D).
- Exanthematous diseases (measles, chickenpox and scarlet fever).
- Congenital syphilis.
- Hypocalcaemia.
- Birth injury, prematurity, Rh haemolytic disease.
- Local infection or trauma.
- Ingestion of chemicals (fluoride).
- Idiopathic causes.
- In mild environmental hypoplasia, there may be only a few small grooves, pits, or fissures on the enamel surface.
- If the condition is more severe, the enamel may exhibit rows of deep pits arranged horizontally across the surface of the tooth.
- There may be only a single row of such pits or several rows indicating a series of injuries.
- In the most severe cases, a considerable portion of enamel may be absent, suggesting a prolonged disturbance in the function of the ameloblasts.
- Hypoplasia results only if the injury occurs during the time of teeth development, or more specifically, during the formative stage of enamel

development.

- Once the enamel has calcified, no such defect can be produced. Thus, knowing the chronological development of the deciduous and permanent teeth, it is possible to determine from the location of the defect on the teeth the approximate time at which the injury occurred.

Hypoplasia due to nutritional deficiency and exanthematous fevers

- Deficiencies of vitamins A, C and D during the time of tooth formation may be the cause of hypoplasia.
- Exanthematous diseases including measles, chickenpox and scarlet fever may also be aetiologic factors for hypoplasia.
- Serious nutritional deficiency or systemic disease is potentially capable of producing enamel hypoplasia, since ameloblasts are one of the most sensitive groups of cells in the body in terms of metabolic function.
- The hypoplasia occurring from these deficiencies or disease states is usually of the pitting variety. Since the pits tend to stain, the clinical appearance of the teeth may be very unsightly.
- Enamel hypoplasia involves those teeth that form within the first year after birth, although teeth that form somewhat later may be affected. Thus, the teeth most frequently involved are the central and lateral incisors, cuspids and first molars.

Enamel hypoplasia due to congenital syphilis

- The hypoplasia due to congenital syphilis is most frequently not of the pitting variety as described previously but instead presents a characteristic, almost pathognomonic appearance.
- This hypoplasia involves the maxillary and mandibular permanent incisors and the first molars.
- The anterior teeth affected are sometimes called *Hutchinson's teeth*, while the molars are referred to as *mulberry molars (Moon's molars, Fournier's molars).*
- Characteristically, the upper central incisor is *screwdriver* shaped, the mesial and distal surfaces of the crown tapering and converging towards the incisal edge of the tooth rather than towards the cervical margin. In addition, the incisal edge is usually notched. The mandibular central and lateral incisors may be similarly involved. The cause of the tapering and

notching of the maxillary incisor has been explained on the basis of the absence of the central tubercle or calcification centre.

- The crowns of the first molars in congenital syphilis are irregular and the enamel of the occlusal surface and occlusal third of the tooth appears to be arranged in an agglomerate mass of globules rather than in well-formed cusps. The crown is narrower on the occlusal surface than at the cervical margin.

Note: Not all patients with congenital syphilis will exhibit the dental findings. Also, occasional patients will appear to have Hutchinson's teeth without having a history of congenital syphilis. Therefore, one must not be hasty in making the diagnosis of syphilis, particularly in the absence of the other conditions of Hutchinson's triad.

Enamel hypoplasia due to hypocalcaemia

- Tetany, induced by a decreased level of calcium in the blood, may result from several conditions, the most common being vitamin D deficiency and parathyroid deficiency.
- In tetany, the serum calcium level may fall as low as 6–8 mg per 100 ml and at this level, enamel hypoplasia is frequently produced in teeth developing concomitantly.
- This type of enamel hypoplasia is usually of the pitting variety and thus does not differ from that resulting from a nutritional disturbance or exanthematous disease.

Hypoplasia due to birth injuries

- The neonatal line or ring was first described by Schour in 1936. It is present in deciduous teeth and first permanent molars, may be thought of as a type of hypoplasia because there is a disturbance produced in the enamel and dentine, which is indicative of trauma or change of environment at the time of birth. In traumatic births, the formation of enamel may even cease at this time.
- Enamel hypoplasia of deciduous teeth involve enamel formed after birth, it is seen also in prenatal enamel. In such instances, a gastrointestinal disturbance or some other illness in the mother may be responsible.

Enamel hypoplasia due to local infection or trauma

- A type of hypoplasia, occasionally seen, is unusual in that only a single tooth is involved, most commonly one of the permanent maxillary incisors or a maxillary or mandibular premolar.
- There may be any degree of hypoplasia ranging from a mild, brownish discolouration of the enamel to a severe pitting and irregularity of the tooth crown. These single teeth are frequently referred to as *Turner's teeth* and the condition is called *Turner's hypoplasia*.
- If a deciduous tooth becomes carious during the period, when the crown of the succeeding permanent tooth is being formed, a bacterial infection involving the periapical tissue of this deciduous tooth may disturb the ameloblastic layer of the permanent tooth and result in a hypoplastic crown.
- The severity of this hypoplasia will depend upon the severity of the infection, the degree of tissue involvement and the stage of permanent tooth formation during which the infection occurred.
- A similar type of hypoplasia may follow trauma to a deciduous tooth, particularly when the deciduous tooth has been driven into the alveolus and has disturbed the permanent tooth bud. If this permanent tooth crown is still being formed, the resulting injury may be manifested as a yellowish or brownish stain or pigmentation of the enamel, usually on the labial surface or as a true hypoplastic pitting defect or deformity.

Enamel hypoplasia due to fluoride (Mottled enamel)

Mottled enamel is a type of enamel hypoplasia that was first described by GV Black and Frederick S McKay in 1916.

Pathogenesis

- ***Aetiology:*** It is now recognized that the ingestion of drinking water containing fluoride during tooth formation may result in mottled enamel.
- The severity of the mottling increases with an increasing amount of fluoride in the water. Thus, there is little mottling of any clinical significance at a level below 0.9–1.0 part per million of fluoride in the water, whereas it becomes progressively evident above this level.
- This type of hypoplasia is due to a disturbance of the ameloblasts during the formative stage of tooth development.
- The exact nature of the injury is unknown, but since there is histologic

evidence of cell damage, it is likely that the cell product, the enamel matrix, is defective or deficient. It has also been shown that, with somewhat higher levels of fluoride, there is interference with the calcification process of the matrix.

Clinical features

- Depending upon the level of fluoride in the water supply, there is a wide range of severity in the appearance of mottled teeth, varying from: (1) *questionable changes* characterized by occasional white flecking or spotting of the enamel, (2) through *mild changes* manifested by white opaque areas involving more of the tooth surface area, (3) to *moderate and severe changes* showing pitting and brownish staining of the surface and even (4) *a corroded appearance* of the teeth.
- Those teeth which are moderately or severely affected may show a tendency for wear and even fracture of the enamel. Also, it is noted that difficulty of retaining restorations in such teeth.

Prognosis and predictive factors

- Mottled enamel frequently becomes stained and unsightly brown colour.
- For cosmetic reasons, it has become the practice to bleach the affected teeth with an agent such as hydrogen peroxide. This is frequently effective, but the procedure must be carried out periodically, since the teeth continue to stain.

Key points

- *Beckwith–Wiedemann syndrome:* Visceromegaly, gigantism, neonatal hypoglycaemia, macroglossia and facial deformities.
- *Fissured tongue:* Down's syndrome and Melkersson–Rosenthal syndrome.
- *Aplasia of salivary gland:* Hemifacial microsomia, LADD syndrome and mandibulofacial dysostosis.
- *Congenital lip pits:* Van der Woude syndrome (cleft lip, cleft palate along with lip pit).
- *Double lip:* Ascher's syndrome (acquired double lip, nontoxic thyroid enlargement, blepharochalasis).
- *Miescher–Melkersson–Rosenthal syndrome:* Cheilitis granulomatosis, facial palsy and scrotal tongue.
- Fordyce's granules are ectopic sebaceous glands that occur on buccal

mucosa.

- *Hypodontia:* The condition of missing up to six teeth, excluding the third molars.
- *Oligodontia:* The condition of missing over six teeth, excluding third molars.
- *Tooth fusion* arises through union of two normally separated tooth germs.
- *Gemination* arises when two teeth develop from one tooth bud.
- *Concrescence* is a condition of teeth where the cementum of two teeth joins together.
- *Taurodontism* is a condition whereby the body of the tooth and pulp chamber is enlarged vertically at the expense of the roots.
- *Natal teeth* are deciduous teeth that have erupted prematurely into the oral cavity at the time of birth in infants.
- *Neonatal teeth* are deciduous teeth that erupt prematurely into the oral cavity within first 30 days after birth.
- Deficiencies of vitamins A, C and D during tooth formation may cause enamel hypoplasia.
- The anterior teeth affected by congenital syphilis are called *Hutchinson's teeth*, whereas the molars are referred to as *mulberry molars* or *Moon's molars* or *Fournier's molars.*
- Enamel hypoplasia of single teeth occurring due to local infection or trauma is referred to as *Turner's teeth* and the condition is called *Turner's hypoplasia*.

Frequently asked questions

1. Development disturbances of tongue.
2. Development disturbances of salivary gland.
3. Development disturbances of lip.
4. Fordyce's granules.
5. Cleft lip and/or cleft palate.
6. Enumerate and discuss the developmental disturbances affecting shape of tooth.
7. Taurodontism.
8. Amelogenesis imperfecta.
9. Dentinogenesis imperfecta.
10. Enamel hypoplasia.

CHAPTER 2

Benign and malignant tumours of the oral cavity

Benign tumours of epithelial tissue origin

Squamous papilloma

Squamous papilloma is generally a benign lesion that arises from the stratified squamous epithelium of the oral cavity.

Pathogenesis

- Squamous papilloma results from infection of human papilloma virus (HPV). The HPV types 6 and 11 are commonly identified.
- The exact mode of transmission is unknown. Transmission may be by sexual and nonsexual person-to-person contact, contaminated objects, saliva and breast milk.
- A latency or incubation period is 3 to 12 months.

Clinical features

- **Age.** 30–50 years.
- **Sex.** No sex predilection.
- **Location.** Tongue, lips, buccal mucosa, gingiva and palate.
- **Signs and symptoms**
 - It is a soft, well circumscribed, pedunculated mass with numerous finger-like surface projections.
 - Oral papillomas are usually painless and not treated unless they interfere with eating or are causing pain.
 - Sometimes, extensive coalescing papillary lesions, *papillomatosis,* of the oral mucosa may be seen in several skin disorders including naevus unius lateris, acanthosis nigricans and Goltz–Gorlin syndrome.

Histopathology (fig. 2.1)

- It is characterized by a proliferation of keratinized stratified squamous epithelium arranged in finger-like (papillary) projections with fibrovascular connective tissue core.
- Connective tissue core is contiguous with stroma of the stalk, the body of the mass and the surface projections.
- Scattered few chronic inflammatory cells are seen in the stroma, presumably from chronic low-grade trauma to the lesion.
- The surface keratin is often quite thickened, usually with parakeratin.

- Koilocytes, virus-altered epithelial clear cells with small dark (pyknotic) nuclei are sometimes seen high in the prickle cell layer.

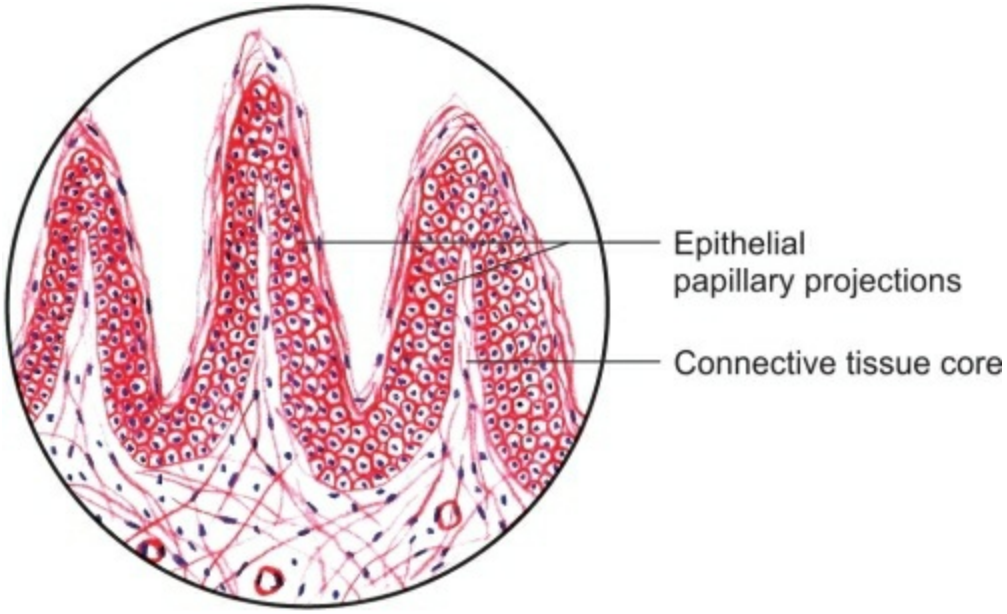


FIG. 2.1 Squamous papilloma.

Prognosis and predictive factors

- Conservative surgical excision including the base of the lesion is adequate treatment for squamous papilloma and recurrence is unlikely.
- Frequently, lesions have been left untreated for years with no reported transformation into malignancy, continuous enlargement or dissemination to other parts of the oral cavity.

Verruca vulgaris

(Synonym: Common wart)

Verruca vulgaris is a benign, viral-induced, focal hyperplasia of stratified squamous epithelium.

Pathogenesis

The HPV types 2, 4, 6 and 40 are associated with verruca vulgaris.

Clinical features

- **Age.** Children but occasionally arise in middle age.
- **Sex.** No sex predilection.
- **Location.** Skin of the hands, oral mucosa—vermillion border, labial mucosa and anterior tongue.
- **Signs and symptoms**
 - Verruca vulgaris is contagious and spread to other parts of a person's skin or mucous membrane by way of autoinoculation.
 - Verruca appears as a white, painless papule or nodule with papillary projections or a rough pebbly surface.
 - Multiple or clustered lesions are common.
 - Extreme accumulation of compact keratin may result in a hard surface projection several millimetres in height, termed as *cutaneous horn* or *keratin horn.*

Histopathology

- It is characterized by proliferation of hyperkeratotic stratified squamous epithelium arranged in finger-like projections with connective tissue cores.
- Chronic inflammatory cells often infiltrate into supporting connective tissue.
- Elongated rete-ridges tend to converge towards the centre of the lesion, producing a cupping effect.
- Koilocytes are often seen in the superficial layer or spinous layer. Koilocytes are HPV-altered epithelial cells with perinuclear clear spaces and small, dark nuclei.

Prognosis and predictive factors

- Surgical excision, cryotherapy, electrosurgery or destruction laser are the different treatment modalities.
- Recurrence is seen in small proportion of treated cases.

Keratoacanthoma

(Synonyms: Self-healing carcinoma; pseudocarcinoma; molluscum sebaceum; keratocarcinoma)

Keratoacanthoma is a self-limiting, epithelial proliferation with a strong clinical and histopathologic similarity to well-differentiated squamous cell carcinoma.

Pathogenesis

- The exact aetiology is unknown.
- Sun damage and HPV types 26 and 37 have been proposed.
- The association with sun damage is suggested by the fact that most solitary lesions are found on sun-exposed skin, predominantly in older adults.
- Contributing factors include tar exposure, immunosuppression, burns and trauma.
- Hereditary predisposition for multiple lesions includes Muir–Torre syndrome (sebaceous neoplasms, keratoacanthomas and gastrointestinal carcinoma). Chromosomal aberrations such as gains on 8q, 1p and 9q with deletions on 3p, 9p, 19p and 19q.

Clinical features

- **Age.** 45 years.
- **Sex.** Male predilection.
- **Location.** Sun exposed areas such as face, neck and upper extremities. In some cases, it occurs on the lips and vermillion border of the upper and lower lips. Intraoral lesions are uncommon.
- **Signs and symptoms**
 - It appears as a firm, non-tender, well-demarcated, sessile, dome-shaped nodule with a central plug of keratin, although intraoral keratoacanthoma usually lacks central plug.
 - The central keratin plug is yellowish, brown or black and has an irregular, crusted often verruciform surface.
 - The evolution of keratoacanthoma can be divided into three phases:
 1. *Growth phase:* Rapid enlargement is typical with lesions usually attaining a diameter of 1–2 cm within 6 weeks.
 2. *Stationary phase:* Lesion stabilizes. Duration is similar to that of growth phase.
 3. *Involution phase:* Most lesions regress spontaneously within 6–12 months of onset, usually leaving a depressed scar in the area. Regression may be due to cytotoxic immune response to the tumour.

Histopathology

- Biopsy should include adjacent, clinically normal epithelium for proper

histopathologic interpretation; this is because the overall pattern of the tumour is diagnostically more important than individual cell appearance.

- The lesion consists of hyperplastic epithelium growing into the underlying connective tissue.
- The surface is covered by a thickened layer of parakeratin or orthokeratin with central plugging.
- The epithelial cells do not usually show atypia but sometimes dyskeratosis and keratin pearl formation is seen.
- Pseudocarcinomatous infiltration typically presents a smooth, regular, well-demarcated front that does not extend beyond sweat glands or underlying muscle.
- The surface epithelium at the lateral edge of the tumour appears normal and elevated towards the central portion of the crater forming acute angle between the overlying epithelium and the lesion; then an abrupt change in the normal epithelium occurs as the hyperplastic acanthotic epithelium is reached (for this reason, the diagnosis is impossible, if the adjacent border of the specimen is not included in the biopsy).
- The crater is filled with keratin, and the epithelium at the base of the crater proliferates downward. This action often elicits a pronounced chronic inflammatory cell response.

Prognosis and predictive factors

- The lesion is treated by surgical excision.
- Prognosis is excellent followed by the excision.

Oral naevi/histopathology of oral naevi/blue naevi

(Synonyms: Oral melanocytic naevus; naevocellular naevus; mole)

The naevi are benign proliferation of naevus cells (neural crest cells) in either epithelium or in the connective tissue.

Naevus cells: These are of neural crest origin and have ability to produce melanin. These represent melanocytes or first cousins of melanocytes. These melanocytic cells migrate to epidermis during development.

Classification

- Naevi are classified as *congenital* or *acquired.*
- Based on histological location of naevus cells, these are classified into three categories:

1. *Junctional naevi:* When naevus cells are limited to the basal cell layer of the epithelium.
2. *Compound naevus:* Naevus cells are in epidermis and dermis.
3. *Intradermal/intramucosal naevus:* Nests of naevus cells entirely in the dermis.

Clinical features

- **Age.** Junctional naevi are first noted in infants. In children and young adults, it is typically matured into compound naevi. In adulthood, the lesion matures into intramucosal naevi.
- **Sex.** Female predilection.
- **Location.** Intradermal naevi occur in waist, head and neck region. Intramucosal naevi occurs in buccal mucosa, mucobuccal fold and gingiva.
- **Signs and symptoms**
 - *Junctional naevus*
 - It is an earliest presentation.
 - Sharply demarcated, brown/black macule, typically less than 6 mm in diameter.
 - It persists same till adulthood.
 - *Compound naevus*
 - Naevus cells proliferate over a period of years to produce slightly elevated, soft papule with relatively smooth surface.
 - As the degree of pigmentation diminishes, it appears brown or tan.
 - *Intradermal naevus*
 - As time passes, naevus gradually loses its pigmentation, the surface may become papillomatous and hairs may be seen growing from centre.
 - Naevus usually remains less than 6 cm in diameter.
 - Ulcerate unless it is traumatized.
 - *Intramucosal naevus*
 - Evolution and appearance similar to skin naevi but mature lesions do not demonstrate a papillary surface change.
 - Asymptomatic lesion.
 - Pigmentation varies from brown to black or blue.
 - Naevi are raised, well circumscribed, round or oval in shape.

Histopathology

- **Naevus cells:** Naevus cells are large, ovoid, rounded or spindle-shaped cells with pale cytoplasm and may contain granules of melanin pigment in their cytoplasm. The nucleus is vesicular and lacks dendritic processes typical of melanocytes. They either lack contact inhibition or lose it shortly after proliferation process begins. Melanosomes retain in naevus cells and are not transferred to adjacent keratinocytes. They tend to be grouped in sheets or cords—nests or theque. Naevus cells also have the ability to migrate from basal cell layer to underlying connective tissue.
- **Junctional naevus:** The zone of demarcation is absent and naevus cells contact and seem to blend into the surface epithelium. The epithelium crossing the junction and growing into the tissue is called *abtropfung* or *dropping off effect*. Transformation of malignant melanomas predominantly occurs in junctional activity.
- **Compound naevus:** It shows features of both the junctional and intradermal naevi. Nests of naevus cells are dropping off from the epidermis, while large nests of naevus cells are also present in dermis.
- **Intradermal or intramucosal naevus:** The naevi cells are situated within the connective tissue and separated from overlying epithelium by a well-defined band of connective tissue.

Blue naevus

(Synonyms: Dermal melanocytoma; Jadassohn–Tieche naevus)

- Blue naevus is of two types—*common blue naevus* and *cellular blue naevus.*
- Blue colour is explained by *Tyndall effect.* It relates to the interaction of light with particles in a colloidal suspension.
- In blue naevus, melanin particles are deep to the surface so that the light reflected back has to pass through the overlying tissue.

Clinical features

Common blue naevus

- **Age.** Children and young adults.
- **Sex.** Female predilection.
- **Location**
 - Mucosal site—hard palate, conjunctiva, sinonasal mucosa.
 - Cutaneous site—dorsal surface of hands and feet, scalp and face.
- **Signs and symptoms.** It appears as macular or dome-shaped, blue or bluish black lesion smaller than 1 cm in diameter.

Cellular blue naevus

- **Age.** Second to forth decades, but it may be congenital also.
- **Sex.** Female predilection.
- **Location.** Sacrococcygeal or buttock region, rarely seen in cutaneous or mucosal surfaces.
- **Signs and symptoms.** Slow-growing blue-black papule or nodule that attains, sometimes, a size of 2 cm or more.

Histopathology

- **Common blue naevus:** It consists of elongated melanocytes with long branching dendritic processes lie in bundles. It orients parallel to the epidermis in the middle and lower third of the dermis. There is no junctional activity.
- **Cellular blue naevus:** It appears as a well-circumscribed, highly cellular aggregation of pump, melanin producing spindle cells within the dermis or submucosa.

These are large, round or spindle cell with pale vacuolated cytoplasm. These cells are commonly arranged in an alveolar pattern.

Prognosis and predictive factors

Surgical excision of all intraoral pigmented naevi is recommended as a prophylactic measure because of constant irritation of the oral mucosa occasioned by eating and tooth brushing.

Potentially malignant disorders (premalignant lesions/conditions)

Premalignant lesions

Oral premalignant lesion was defined by World Health Organization (*WHO)* in *1972* as a "morphologically altered tissue in which cancer is more likely to occur than its apparently normal counterpart".

- Leukoplakia
- Erythroplakia
- Palatal keratosis associated with reverse smoking
- Solar keratosis

Precancerous conditions

Oral precancerous condition is defined as a *generalized state associated with a significantly increased risk of cancer.*

- Oral submucous fibrosis
- Lichen planus
- Sideropenic dysphagia
- Syphilis
- Xeroderma pigmentosum
- Discoid lupus erythematosus
- Dyskeratosis congenital
- Epidermolysis bullosa

The lesion and condition share the same aetiological factors with oral cancer, particularly use of tobacco. Premalignancy is not guaranteed to transform into cancer. The individual with premalignancy has high risk of developing oral cancer as compared to tobacco users who do not have precancer.

Epithelial dysplasia

Dysplasia means *disordered growth*. Dysplasia is encountered principally in epithelia and is characterized by a constellation of changes that include loss of uniformity of individual cells as well as loss in their architectural orientation.

WHO in 2005 recommended to abandon the traditional distinction between premalignant lesions and premalignant conditions and to use the term *potentially malignant disorders* instead (Table 2.1). Van der Waals reported that

despite of tremendous progress in molecular biology, there is still no marker that reliably predicts malignant transformation in an individual patient.

Table 2.1
Potentially malignant disorder

Approximate malignant potential	Disorder
Very high	Erythroplakia
High	Actinic cheilitis Candidal leukoplakia (candidiasis) Dyskeratosis congenita Proliferative verrucous leukoplakia Sublingual keratosis Submucous fibrosis Syphilitic leukoplakia Xeroderma pigmentosum
Low	Atypia in immunocompromised patients Diabetes Discoid lupus erythematosus Fanconi syndrome Leukoplakia (homogenous) Lichen planus Paterson–Kelly–Brown syndrome Scleroderma

Leukoplakia

The term *leukoplakia* originates from two Greek words: *leuko*—white, *plakia*—patch. Leukoplakia is defined as *a whitish patch or plaque that cannot be characterized, clinically or pathologically as any other disease and is not associated with any other physical or chemical causative agent except the use of tobacco* (Axell et al, 1984).

Aetiology

- Tobacco (dried leaves of *Nicotiana tabaccum*)
- Tobacco is widely used in two forms:
 1. Smokeless tobacco—chewable tobacco
 2. Smoking tobacco—cigar, beedi and pipe

Smokeless tobacco: The extract of tobacco contains various chemical constituents such as nitrosonornicotine, nicotine, pyridine and picoline and colliding materials. These extracts produce sublethal cell injury within deeper layers of oral epithelium.

Smoking tobacco: It is harmful as this smoke contains polycyclic hydrocarbons, beta naphthylamine, nitrosamines, carbon monoxide, nicotine, which act as source of irritation. The heat produced by

smoking tobacco also plays a major role in alteration of tissue.

Alcohol: It causes irritation and burning sensation of oral mucosa, when applied locally. Alcohol facilitates the entry of carcinogen into exposed cells and thus alters the oral epithelium and its metabolism.

Sanguinaria: This is a herbal extract used in toothpaste and mouth rinse.

Chronic irritation: The source of irritation or trauma may be any malocclusion—ill-fitting dentures, sharp broken teeth and hot spicy food.

Galvanism or electromagnetic reaction: Galvanism is the generation of electric current due to difference in the electrical potential of two dissimilar metals. Galvanic current may arise in mouth between dissimilar opposing metallic restorations. Due to chronic irritation of adjacent oral mucosa, it may promote malignant transformation of leukoplakia.

Other aetiological factors are vitamin deficiency, xerostomia, drugs such as anticholinergics, antimetabolics may predispose to leukoplakia.

Clinical findings

- **Age.** 35–45 years.
- **Gender.** Males predilection.
- **Location.** Buccal mucosa, commissures, lip and tongue.
- **Signs and symptoms**
 - *Homogenous leukoplakia (thick leukoplakia).* It appears as well-defined white patch, localized or extensive, that is slightly elevated and that has a fissured, wrinkled or corrugated surface. On palpation, these lesions may feel leathery to dry or cracked mud-like. These lesions may be smooth, furrowed (fissured) or ulcerated.
 - *Non-homogenous leukoplakia (nodular or speckled leukoplakia).* It is a well-demarcated raised white lesion, interspersed with reddened areas in which keratotic white nodules or patches are distributed over an atrophic erythematous background. This type of leukoplakia is associated with a higher malignant transformation rate. On palpation, the lesion may be finely granular, roughened, nodular or indurated.
 - *Proliferative verrucous leukoplakia (PVL)* is characterized by the development of multiple keratotic plaques with roughened surface projections. Although the lesions typically begin as a simple, flat hyperkeratosis that are indistinguishable from ordinary leukoplakic

lesions, PVL exhibits persistent growth, eventually becoming exophytic and verrucous in nature.

As the lesions progress, they may go through a stage indistinguishable from verrucous carcinoma, but they later usually develop dysplastic changes and transform into full-fledged squamous cell carcinoma.

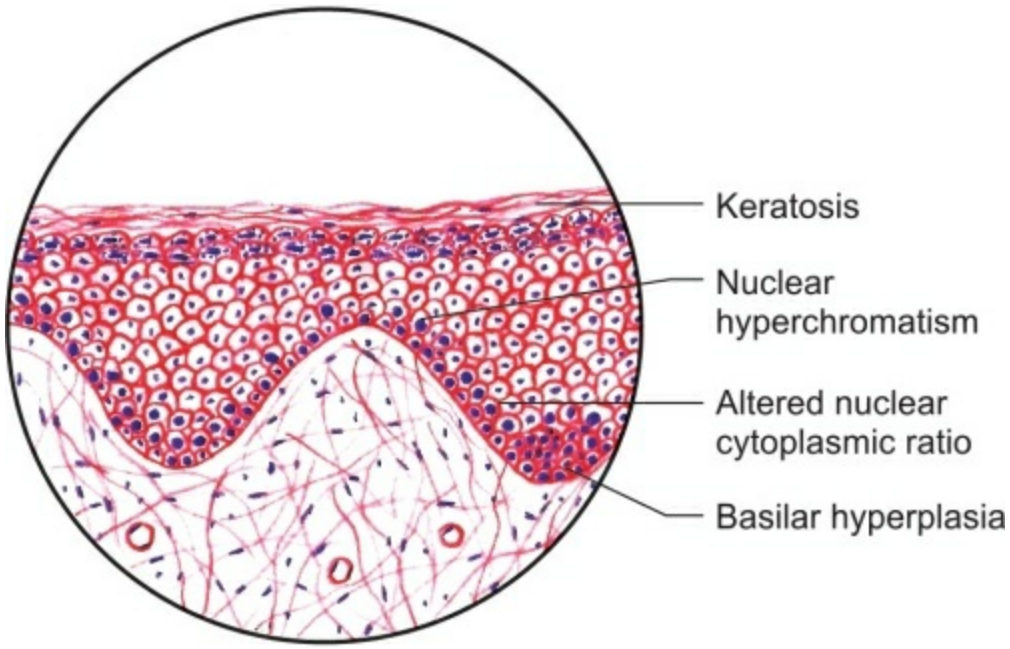
Histopathology

- Leukoplakia is characterized by a thickened keratin layer of the surface epithelium (hyperkeratosis), with or without a thickened spinous layer (acanthosis).
- The keratin layer may consist of parakeratin (hyperparakeratosis), orthokeratin (hyperorthokeratosis) or combination of both. With parakeratin, there is no granular cell layer and the epithelial nuclei are retained in the keratin layer. With orthokeratin, the epithelium demonstrates a granular cell layer and the nuclei are lost in the keratin layer.
- The histopathological criteria used for diagnosing dysplasia:

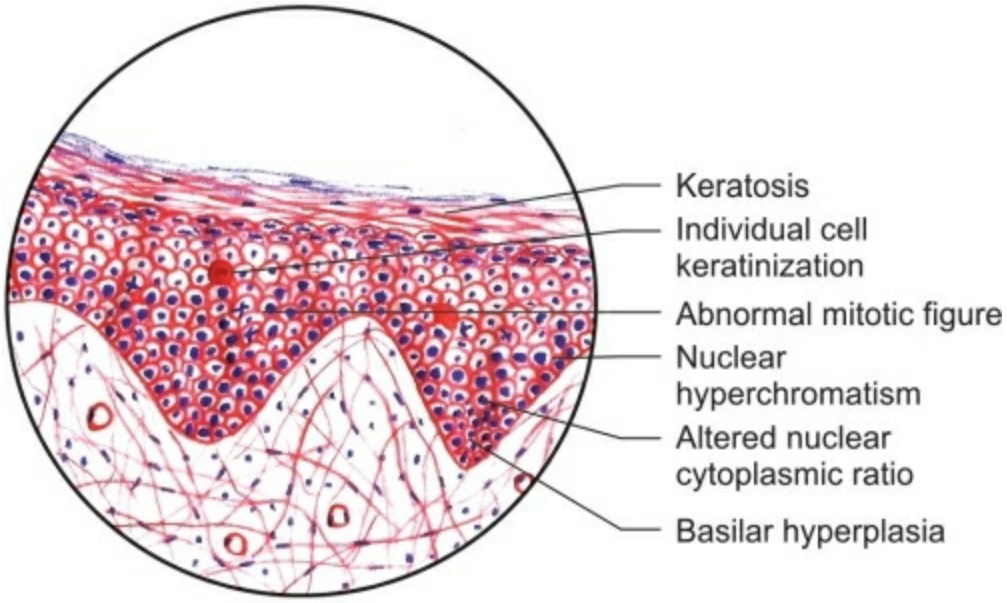
 Architecture
 - Irregular epithelial stratification
 - Loss of polarity of basal cells
 - Drop-shaped rete ridges
 - Increased number of mitotic figures
 - Abnormal superficial mitoses
 - Premature keratinization in single cells (dyskeratosis)
 - Keratin pearls within rete ridges

 Cytology
 - Abnormal variation in nuclear size (anisonucleosis)
 - Abnormal variation in nuclear shape (nuclear pleomorphism)
 - Abnormal variation in cell size (anisocytosis)
 - Abnormal variation in cell shape (cellular pleomorphism)
 - Increased nuclear: cytoplasmic ratio
 - Increased nuclear size
 - Atypical mitotic figures
 - Increased number and size of nucleoli
 - Hyperchromasia
- **Epithelial dysplasia is classified according to the severity** (Fig. 2.2a–c)
 - *Mild epithelial dysplasia* (Fig. 2.2a) refers to alteration limited principally to the basal and parabasal layers.

- *Moderate epithelial dysplasia* (Fig. 2.2b) demonstrates involvement from the basal layer to the mid-portion of the spinous layer.
- *Severe epithelial dysplasia* (Fig. 2.2c)demonstrates alterations from the basal layer to a level above the mid-portion of the epithelium.
- When entire thickness epithelium is involved, the term *carcinoma in situ* is used.



(a)



(b)

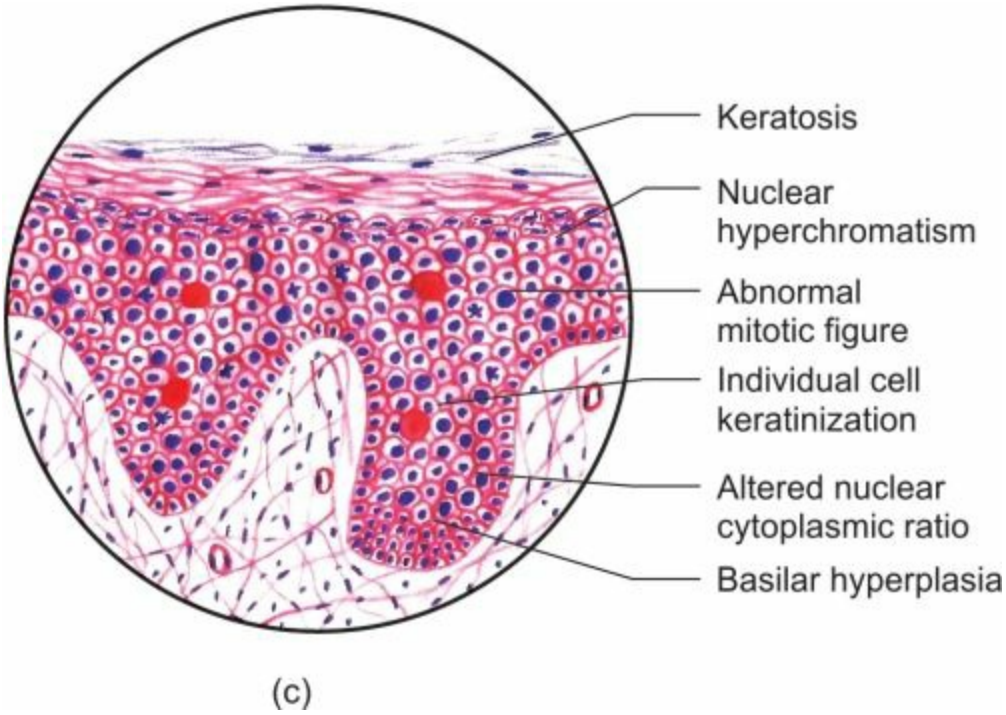


FIG. 2.2 Epithelial dysplasia: (a) Mild; (b) moderate; (c) severe.

Prognosis and predictive factors

- Leukoplakia with mild or minimal dysplasia may disappear or diminish in size within 3 months after the patient stops smoking, thus habit cessation is recommended.
- Complete removal can be accomplished with equal effectiveness by surgical excision, electrocautery and cryosurgery or laser ablation. Long-term follow-up is extremely important because recurrence is frequent.

Erythroplakia

(Synonyms: Erythroplasia; erythroplasia of Queyrat)

Erythroplakia is a bright red velvety plaque which cannot be characterized clinically or pathologically as due to any other condition.

Almost all true erythroplakias demonstrate significant epithelial dysplasia, and carcinoma in situ.

Pathogenesis

The causes of erythroplakia are unknown, but extrinsic factors such as tobacco, alcohol, syphilis, sunlight and intrinsic factors such as malnutrition are also considered as aetiological factors.

Clinical features

- **Age.** 64–75 years.
- **Gender.** No sex predilection.
- **Location.** The floor of the mouth, buccal mucosa, tongue and soft palate.
- **Signs and symptoms.** There are three different clinical manifestations of erythroplakia in the oral cavity:
 1. The homogenous form which appears bright red, soft velvety lesion with straight or scalloped well-demarcated margins.
 2. Erythroplakia interspersed with patches of leukoplakia in which the erythematous areas are irregular and are referred to as *erythroleukoplakia*.
 3. Soft, red lesions that are slightly elevated with an irregular outline and a granular or finely nodular surface speckled with tiny white plaques often referred to as *speckled erythroplakia*.

Histopathology

- It represents either severe epithelial dysplasia or carcinoma in situ.
- The epithelial aspect shows a lack of keratin production and often is atrophic, but it may be hyperplastic. This lack of keratinization, especially when combined with epithelial thickness, allows the underlying microvasculature to show through, thereby explaining the red colour.
- The underlying connective tissue often demonstrates chronic inflammation.

Prognosis and predictive factors

- The treatment of erythroplakia is guided by definitive diagnosis obtained by biopsy.
- Lesions exhibiting moderate dysplasia must be removed completely.
- Recurrence and multifocal oral mucosal involvement are common with erythroplakia, so long-term follow-up is suggested for treated patients.

Nicotine stomatitis

(Synonyms: Nicotina palati; smoker's palate)

- A common mucosal change of the hard palate due to cigar and pipe smoking is referred as *nicotine stomatitis.*
- In some South American and South-East Asian cultures, hand-rolled cigarettes and cigars are smoked with lit end held within the mouth.

These *reverse smoking* habits produce a pronounced palatal keratosis or reverse smoker's palate, which has significant potential to develop dysplasia or carcinoma.

Clinical features

- **Age.** >40 years.
- The palatal mucosa becomes diffusely grey or white due to long-term exposure to heat, numerous slightly elevated papules are noted, usually with red punctuate and red centres.
- Such papules represent the inflamed minor salivary glands and their ductal orifices.
- The palatal keratin may become so thickened that a fissured appearance is imparted.
- The whiteness usually involves marginal gingiva and interdental papillae.

Histopathology

- Nicotine stomatitis is characterized by hyperkeratosis and acanthosis of the palatal epithelium and mild, patchy, chronic inflammation of subepithelial connective tissue and mucous glands.
- Squamous metaplasia of the excretory ducts is usually seen and an inflammatory exudate may be noted within the duct lumina.
- Epithelial dysplasia is rarely seen.

Prognosis and predictive factors

- The palate returns to normal, usually within 1–2 weeks of smoking cessation.

Oral submucous fibrosis (fig. 2.3)

Definition

Oral submucous fibrosis (OSMF) is defined as a chronic insidious disease affecting any part of the oral cavity and sometimes pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory reaction followed by fibroelastic change of the lamina propria with epithelial atrophy leading to stiffness of the oral mucosa causing trismus and difficulty in eating (Pindborg, 1966).

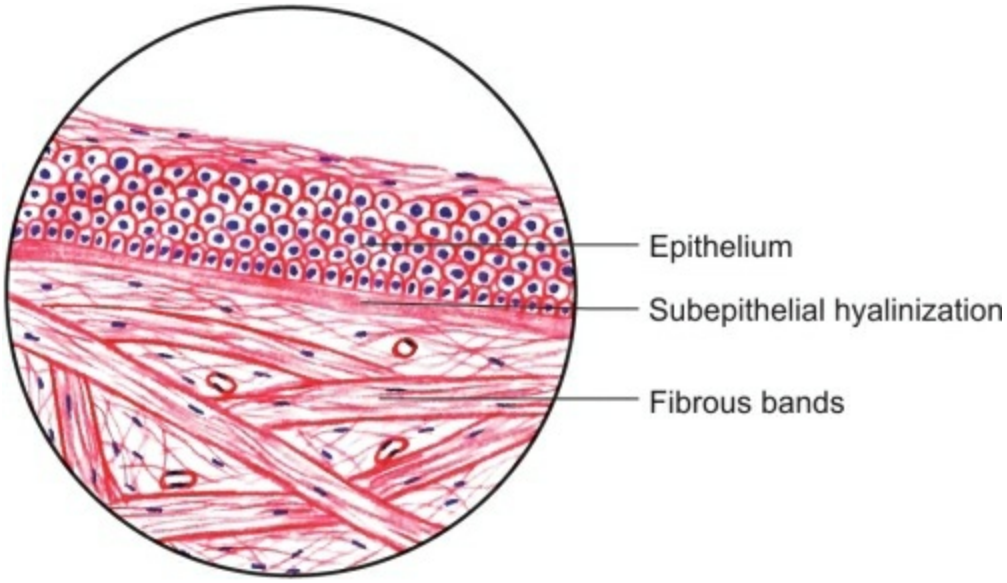
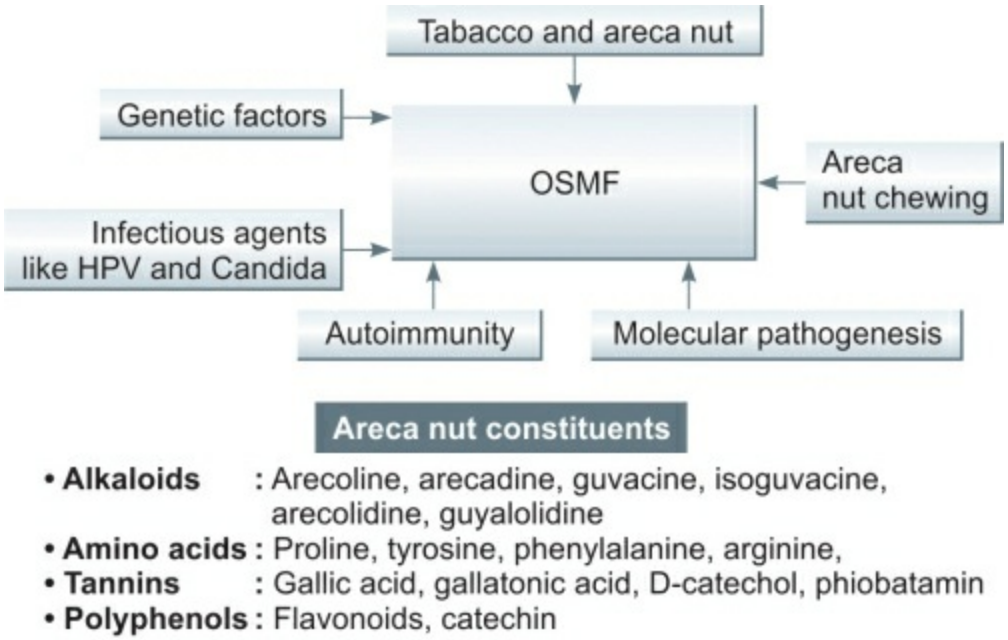


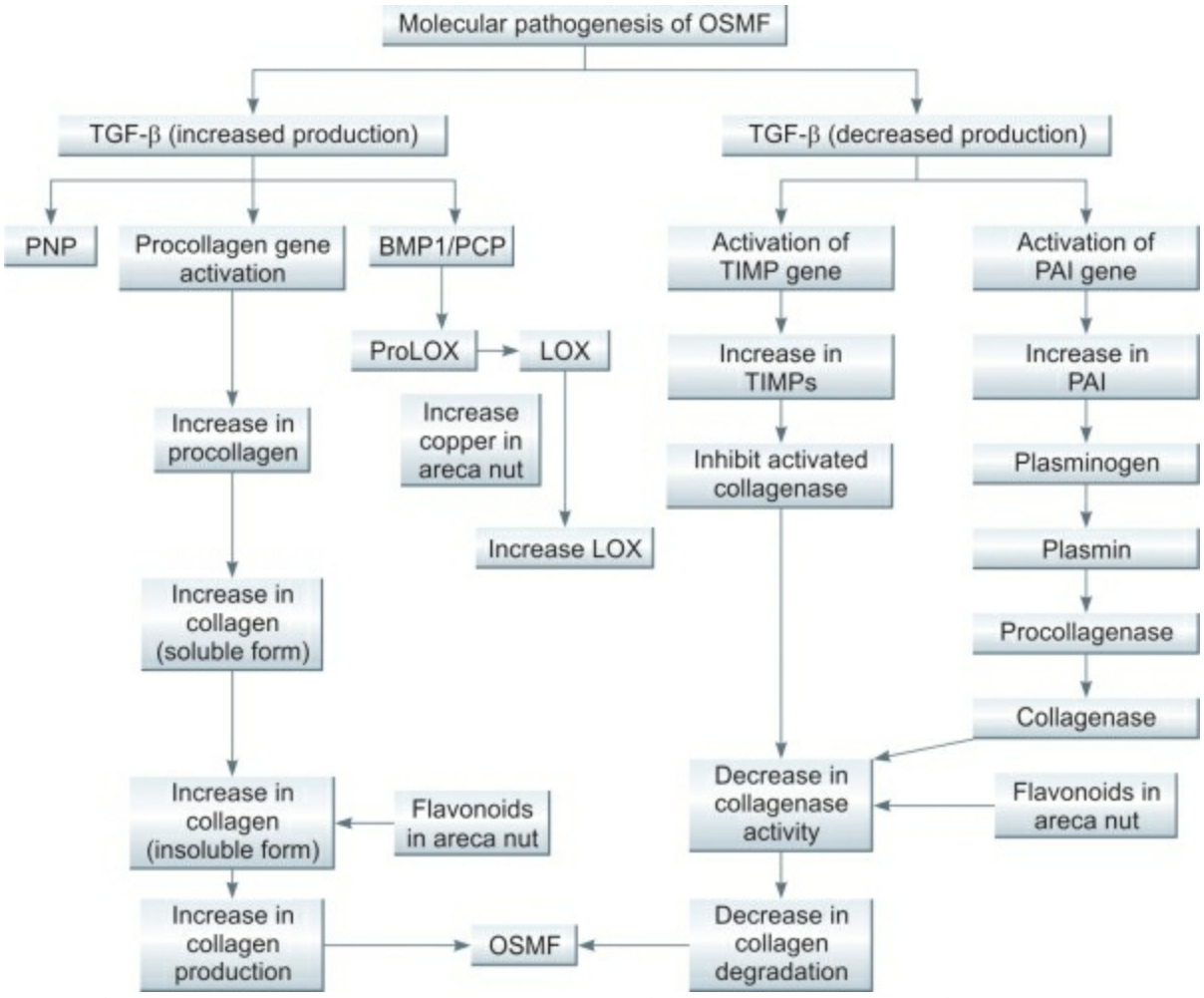
FIG. 2.3 Oral submucous fibrosis.

Pathogenesis (flowcharts 2.1 and 2.2)

- Chronic placement of a *betel quid* or *pan* in the mouth.
- *Betel nut and lime:* Lime is used with betel nut for chewing; it causes local irritation and damage to the mucosa with vesicle and ulcer formation in susceptible individuals. It acts as a local irritant.
- Betel nut has psychotropic and antihelminthic property due to the presence of areca alkaloids, predominantly are coline. These alkaloids have powerful parasympathetic properties which produce euphoria and counteract fatigue.



FLOWCHART 2.1 Pathogenesis of oral submucous fibrosis



FLOWCHART 2.2 Molecular pathogenesis of OSMF (**TGF-β:** Transforming growth factor-beta; **PNP:** Procollagen N-proteinase; **BMP1:** Bone morphogenetic protein 1; **PCP:** Procollagen C-proteinase; **LOX:** Lysyl oxidase; **PAI:** Plasminogen activator inhibitor; **TIMP:** Tissue inhibitor of matrix metalloproteinase)

Clinical features

- **Age.** 20–40 years.
- **Gender.** No sex predilection.
- **Location.** Buccal mucosa, retromolar area, soft palate, palatal fauces, uvula, tongue and labial mucosa. Rarely involves floor of the mouth and gingiva.
- **Signs and symptoms**
 - The initial symptoms are burning sensation of oral mucosa, aggravated by spicy food, hypersalivation and dryness of mouth.
 - Vesiculation, ulceration, pigmentation, recurrent stomatitis and defective gustatory sensation.
 - The late symptoms are trismus (inability to open the mouth) due to

gradual stiffening of oral mucosa. When tongue is involved, there is difficulty in protruding the tongue.
- The mucosa eventually blanched and opaque and fibrotic bands appear usually involving the buccal mucosa, soft palate, lips and tongue.

Histopathology

- The oral epithelium is invariably atrophic with complete loss of rete ridges.
- The underlying connective tissue shows severe hyalinization with homogenization of collagen bundles.
- Fibroblasts are markedly diminished in number and the blood vessels are completely obliterated or narrowed.

Prognosis and predictive factors

- Discontinuation of habit helps in gradual increase in inter-incisal opening.
- **Steroids**
 - *Local:* Hydrocortisone injection with procaine hydrochloride injection locally in the area of fibrosis.
 - *Systemic:* A therapy with hydrocortisone 25 mg tablet, in doses of 100 mg per day is useful in relieving burning sensation. Triamcinolone or 90 mg of dexamethasone can be given.
- **Supportive treatment:** Vitamin-rich diet and iron supplements.
- **Hyaluronidase:** It shows improvement in trismus, burning sensation and health of mucosa.
- **Surgical:** Surgical splitting or excision of fibrous bands may improve mouth opening and mobility in the later stages of diseases.

Malignant tumours of epithelial tissue origin

Squamous cell carcinoma

(Synonym: Epidermoid carcinoma)

Squamous cell carcinoma is defined as *a malignant epithelial neoplasm exhibiting squamous differentiation as characterized by the formation of keratin and/or the presence of intercellular bridges* (Pindborg et al, 1997).

Pathogenesis

- The cause of oral squamous cell carcinoma is multifactorial. It is likely that more than a single factor is needed to produce such a malignancy (carcinogenesis).
- Extrinsic factors include external agents, e.g. tobacco smoking, alcohol, syphilis and sunlight.
- Intrinsic factors include systemic or generalized states, e.g. malnutrition and iron deficiency anaemia.
- Many oral squamous cell carcinomas have been documented to be associated with or preceded by a precancerous lesion, especially leukoplakia.

 Tobacco smoking: Much indirect clinical evidence implicates the habit of tobacco smoking in the development of oral squamous cell carcinoma. The proportion of smokers (80%) among patients with oral carcinoma is 2–3 times greater than general population.

 Smokeless (spit) tobacco: Smokeless tobacco increases a chronic user's risk for oral carcinoma.

 Betel quid: The betel quid or paan is a compound of natural substance chewed for psycho- stimulating effects. This habit is also associated with significant development of precancerous lesions, e.g. leukoplakia.

 Alcohol: Alcohol consumption and abuse, in and of itself, has not been definitively proven to be capable of initiating oral cancer. Case control studies have concluded that the risk is dose dependent and time dependent and the combination of alcohol and tobacco abuse over long period may increase a person's risk for oral carcinoma.

 Radiation: The effect of irradiation decreases immune reactivity and produces abnormalities in chromosomal material. Radiotherapy to the head and neck area increases the risk of the later development of a new primary oral malignancy, either a carcinoma or sarcoma.

Iron deficiency: Iron deficiency, especially the severe, chronic form known as the Plummer–Vinson or Paterson–Kelly syndrome, is associated with an elevated risk for squamous cell carcinoma of the oropharynx and posterior mouth. People who are deficient in iron tend to have impaired cell-mediated immunity, and iron is essential to the normal functioning of epithelial cells. In deficiency states, these epithelial cells turn over more rapidly and produce an atrophic or immature mucosa.

Syphilis: Syphilis has long been accepted as having a strong association with the development of dorsal tongue carcinoma. The arsenicals and heavy metals that were used to treat syphilis before the advent of modern antibiotics have carcinogenic properties themselves and may have been responsible for some of the earlier carcinoma development in this disease.

Candidal infection: Some strains of *Candida albicans* have produced hyperkeratotic lesions of the dorsal part of tongue without any other contributing factor. Certain strains have been shown to produce nitrosamines, chemicals that have been implicated in carcinogenesis.

Oncogenic viruses: Oncogenic viruses may play a major role in a wide variety of cancers, although no virus has definitively been proven to cause oral cancer so far. Viral agents capable of integration into host genetic material may be particularly dangerous and potentially could commander the host ability to regulate normal growth and proliferation of the infected cell. The oncogenic viruses may immortalize the host cell, thereby facilitating malignant transformation. HPV subtypes 16, 18, 31 and 33 are the strains most closely associated with dysplasia and squamous cell carcinoma.

Immunosuppression: Immunosuppression may play a role in development of at least some malignancies of the upper aerodigestive tract.

Clinical features

- Oral squamous cell carcinomas most often occur in older men.
- There is minimal pain during the early growth phase.
- Oral squamous cell carcinoma has a varied clinical presentation, including:
 - Exophytic (mass forming: fungating, papillary, verruciform)
 - Endophytic (invasive, burrowing, ulcerated)
 - Leukoplakic (white patch)

 - Erythroplakic (red patch)
 - Erythroleukoplakic (combined red and white patch)
- The *leukoplakic* and *erythroplakic* are probably early cases that have not yet produced a mass or ulceration, and the clinical features are identical to those described for premalignant leukoplakia and erythroplakia. These mucosal surface changes typically are destroyed by the developing exophytic or endophytic carcinoma, but many cases are diagnosed before their complete destruction and show residual precancerous lesions involving adjacent mucosa.
- An *exophytic lesion* has a surface that is irregular, fungating, papillary or verruciform and its colour may vary from normal to red to white depending on the amount of keratin and vascularity. The surface is often ulcerated and the tumour feels indurated on palpation.
- An *endophytic growth* pattern is characterized by a depressed, irregularly shaped, ulcerated, central area with a surrounding *rolled* border of normal, red or white mucosa. The rolled border results from invasion of the tumour downward and laterally under the adjacent epithelium.
- Destruction of underlying bone, when present, may be painful or completely painless and it appears on radiographs as a *moth-eaten* radiolucency with ill-defined or ragged margins. Carcinoma also can extend for many centimetres along a nerve (perineural invasion) without breaking away to form a true metastasis.
- *Metastasis:* The metastatic spread of oral squamous cell carcinoma is largely through the lymphatics to the ipsilateral cervical lymph nodes. A cervical lymph node that contains a metastatic deposit of carcinoma is usually firm to stony hard, non-tender and enlarged. If the malignant cells have perforated the capsule of the node and invaded into surrounding tissue, the node will feel fixed or not easily movable.

Carcinoma of the lower lip and oral floor tends to travel to the submental nodes; tumours from the posterior portions of the mouth travel to the superior jugular and diagastric nodes. Lymphatic drainage from the oropharynx leads to the jugulodigastric chain of lymph nodes and metastatic deposits from oropharyngeal carcinoma are usually found there.

Staging

- Tumour size and the extent of metastatic spread of oral squamous cell carcinoma are the best indicators of the patient's prognosis.
- Quantifying these clinical parameters is called *staging the disease*.

- This staging protocol depends on three basic clinical features:
 1. **T:** Size of the primary tumour, in centimetres
 2. **N:** Involvement of local lymph nodes
 3. **M:** Distant metastasis

Tumour node metastasis (TNM) staging system for oral carcinoma (table 2.2)

Primary tumour size (T)

- **Tx:** No available information on primary tumour
- **T0:** No evidence of primary tumour
- **T1s:** Only carcinoma in situ at primary site
- **T1:** Tumour less than 2 cm in greater diameter
- **T2:** Tumour is 2–4 cm in greatest diameter
- **T3:** Tumour is more than 4 cm in greatest diameter
- **T4:** Massive tumour greater than 4 cm in diameter with involvement of antrum, pterygoid muscles, base of the tongue or skin.

Table 2.2

TNM clinical staging categories for oral squamous cell carcinoma

Stage	TNM classification
Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T3N0M0
	T1, T2 or T3, N1M0
Stage IV	Any T4 lesion,
	Any N2 or N3 lesion or M1 lesion

Regional lymph node involvement (N)

- **Nx:** Nodes could not be or were not assessed
- **N0:** No clinically positive nodes
- **N1:** Single clinically positive homolateral nodes less than 3 cm in diameter
- **N2:** Single clinically positive homolateral nodes less than 3–6 cm in diameter or multiple clinically homolateral nodes, not more than 6 cm in diameter
 - **N2a:** Single clinically positive homolateral node 3–6 cm in diameter
 - **N2b:** Multiple clinically positive homolateral nodes, not more than 6 cm

in diameter
- **N3:** Massive homolateral node or nodes, bilateral nodes or contralateral node or nodes
 - **N3a:** Clinically positive homolateral node or nodes, not more than 6 cm in diameter
 - **N3b:** Bilateral clinically positive nodes
 - **N3c:** Contralateral clinically positive node or nodes

Involvement by instant metastases (M)

- **Mx:** Distant metastasis was not assessed
- **M0:** No evidence of distant metastasis
- **M1:** Distant metastasis is present.

Histopathology

- Squamous cell carcinoma arises from dysplastic surface epithelium and is characterized histopathologically by invasive islands and cords of malignant squamous epithelial cells.
- Invasion is represented by irregular extension of lesional epithelium through basement membrane and into subepithelial connective tissue.

Individual squamous cells and sheet or islands of cells are seen to be thriving as independent entities within the connective tissue without attachment to the surface epithelium.

- Invading cells and cell masses may extend deeply into underlying adipose tissue, muscle or bone, destroying the original tissue as they progress.
- Lesional cells may surround and destroy blood vessels, which may invade into the lumina of veins or lymphatics.
- A strong inflammatory or immune cell response to invading epithelium and focal areas of necrosis may be present.
- The lesional epithelium is capable of inducing the formation of new blood vessels, *angiogenesis,* dense fibrosis, *desmoplasia* or *scirrhous change.*
- Whether the tumour is superficially or deeply invasive, lesional cells generally show abundant eosinophilic cytoplasm with large darkly staining (hyperchromatic) nuclei and an increased nuclear: cytoplasmic ratio with varying degrees of cellular and nuclear pleomorphism.
- Keratin pearls, a round focus of concentrically layered keratinized cells, may be produced within lesional epithelium.
- Histopathologic evaluation of the degree to which these tumours resemble their parent tissue (squamous epithelium) and produce their normal

https://t.me/RoyalDentistryLibrary/

product (keratin) is called *grading.*

- ***Well-differentiated neoplasm***
 - It closely resembles its parent tissue (squamous epithelium).
 - Sheets and nests of cells are seen.
 - These cells are large and show a distinct cell membrane with intercellular bridges.
 - The nuclei of neoplastic cells are large and hyperchromatic.
 - Individual cell keratinization and formation of keratin pearls of varying size are seen.
 - These malignant cells can be found actively invading the connective tissue in a varying pattern.
- ***Moderately differentiated neoplasm***
 - Its resemblance to squamous epithelium is less pronounced.
 - The characteristic shape of the cells and their arrangement may be altered.
 - The growth rate of the individual cells is more rapid and this is reflected in the greater number of mitotic figures.
 - Greater variation in size, shape and the failure to carry out the function of differentiated squamous cell, the formation of keratin.
- ***Poorly differentiated neoplasm***
 - It has little resemblance to its cell of origin.
 - It presents diagnostic difficulties because of primitive and uncharacteristic histologic appearance of the malignant rapidly dividing cells.
 - These cells show a greater lack of cohesiveness and are extremely vagarious.

Carcinoma of lip

Pathogenesis

- Carcinoma of the lip vermillion is typically found in light-skinned persons with either long-term exposure to ultraviolet radiation from sunlight or history of acute sun damage early in life.
- It is usually associated with actinic cheilosis and may arise at the site where cigar or pipe stem is held by the patient.

Clinical features

https://t.me/RoyalDentistryLibrary/

- **Age.** 55–75 years.
- **Gender.** Male predilection.
- **Location.** Upper lip is commonly involved.
- **Signs and symptoms**
 - It depends upon the duration of lesion and nature of growth. Initially, small area of thickening, induration and ulceration or irregular surface is seen. Later, the lesion becomes larger and it may create a small crater-like defect or produces an exophytic proliferative growth of tumour tissue.
 - The typical vermillion carcinoma is crusted, oozing, non-tender, indurated ulceration that is usually less than 1 cm.
 - Metastasis is a late event; at diagnosis fewer than 2% of patients have metastatically involved lymph nodes, usually in the submental region. Perineural invasion may result in extension of the tumour into the mandible through mental foramen.

Histopathology

- Most of the lesions are well-differentiated lesions.
- Usually, they metastasize late in the course of disease.

Prognosis and predictive factors

Although this tumour is diagnosed and treated at early stage, the patient's neglect can result in considerable destruction of normal tissue.

Carcinoma of the tongue

Pathogenesis

The development of carcinoma of the tongue includes tobacco, alcohol and chronic trauma.

Clinical features

- The most common sign of carcinoma of tongue is a painless mass or ulcer, although in most patients, the lesion ultimately becomes painful, when it is secondarily infected.
- The tumour may begin as a superficially indurated ulcer with slightly raised borders and may proceed either to develop a fungating, exophytic mass or to infiltrate the deep layers of the tongue, producing fixation and

https://t.me/RoyalDentistryLibrary/

induration without much surface change.

- The typical lesion develops on the lateral border or ventral surface of the tongue. In rare cases, carcinoma occurs on the dorsum of the tongue; it is usually in a patient with a past or present history of syphilitic glossitis.
- Lesions near the base of the tongue are particularly insidious, since they may be asymptomatic until far advanced. The lesions on the posterior portion of the tongue usually metastasize earlier and offer poorer prognosis.
- Metastases occur with great frequency in cases of tongue carcinoma.

Prognosis and predictive factors

The treatment of tongue carcinoma is difficult, even though surgical excision and radiation therapy are indicated. Metastatic nodes are highly complicating factors in prognosis.

Carcinoma of floor of the mouth

Pathogenesis

Smoking, especially a pipe and cigars, is considered as aetiological factor.

Clinical features

- The carcinoma is indurated and ulcer of varying size is situated on one side of the midline.
- It may or may not be painful.
- More frequently occurs in the anterior portion of floor of the mouth. Because of its location, early extension into the lingual mucosa of the mandible and into the mandible proper as well as into the tongue occurs with considerable frequency.
- Carcinoma of the floor of the mouth may invade the deeper tissues and may even extend into the submaxillary and sublingual glands.
- The proximity of this tumour to the tongue, producing some limitation of motion of tongue, often induces a peculiar thickening or slurring of the speech.
- Metastases from floor of the mouth are found most commonly in the submaxillary group of lymph nodes and since the primary lesion frequently occurs near the midline, where a lymphatic cross-drainage exists, contralateral metastases are often present.

https://t.me/RoyalDentistryLibrary/

Prognosis and predictive factors

Even small tumours are apt to recur after surgical excision, for this reason, radiation therapy gives far better results than surgery.

Carcinoma of buccal mucosa

Pathogenesis

- Several factors are considered as aetiological agents but the use of tobacco and the habit of chewing betel nut play a significant role.
- Leukoplakia is a common predecessor of carcinoma of buccal mucosa. It is usually of extremely long duration and may or may not necessarily be associated with the use of tobacco.

Clinical features

- The lesions develop most frequently along or inferior to a line opposite the plane of occlusion.
- The anteroposterior position is variable, some cases occurring near the third molar area, whereas others forward towards the commissure.
- The lesion is often painful and ulcerative, which shows induration and infiltration into deeper tissues.
- The incidence of metastases is relatively high.

Prognosis and predictive factors

Combination of surgical excision and radiotherapy is indicated.

Carcinoma of gingiva

Pathogenesis

The aetiology of carcinoma of the gingiva appears to be no specific or defined than that in other areas of the oral cavity.

Clinical features

- Carcinoma of mandibular gingiva is more common than involvement of maxillary gingiva.
- Carcinoma of gingiva usually manifested initially as an area of ulceration which may be purely erosive lesion or may exhibit an exophytic, granular

https://t.me/RoyalDentistryLibrary/

or verrucous type of growth.

- It may or may not be painful.
- The tumour arises more commonly in edentulous areas, although it may develop in dentulous area.
- The attached gingiva is more frequently involved.
- In the maxilla, gingival carcinoma often invades into maxillary sinus, palate and tonsillar pillar.
- In the mandible, carcinoma extends into floor of the mouth and the bone.
- Pathological fractures occur in the latter instance.
- Metastasis is more common.
- Cancer of mandibular gingiva occurs more frequently than the maxillary gingival carcinoma.

Prognosis and predictive factors

Combination of surgical excision and radiotherapy is indicated.

Carcinoma of palate

Carcinoma of palate is not a common lesion of oral cavity.

Pathogenesis

Reverse smoking.

Clinical features

- It is poorly defined, ulcerated, painful lesion on one side of the midline. It extends laterally to the gingiva and posteriorly to involve tonsillar pillar.
- The tumour on the hard palate may invade into the bone or occasionally into the nasal cavity while infiltrating lesions of the soft palate may extend into the nasopharynx.
- Metastasis to regional lymph nodes may occur. Metastasis of carcinoma of soft palate is more common than carcinoma of hard palate.

Prognosis and predictive factors

Combination of surgical excision and radiotherapy is indicated.

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma refers to malignancies that arise from the lining

https://t.me/RoyalDentistryLibrary/

epithelium of the pharyngeal tonsils, palatine tonsil and lingual tonsils. These three anatomic sites are collectively called *Waldeyer's tonsillar tissue* or *Waldeyer's ring*.

Pathogenesis

- Exact aetiology is unknown.
- Infection with Epstein–Barr virus.
- Diets deficient in vitamin C.
- Consumption of salt fish that contains potentially carcinogenic nitrosamines.

Clinical features

- **Age.** 40–60 years.
- **Gender.** Male predilection.
- **Location.** Nasopharyngeal mucosa.
- **Signs and symptoms**
 - The primary lesion arises from the lateral nasopharyngeal wall, often is small and difficult to detect.
 - The first sign of disease is an enlarged, firm to hard, cervical lymph node, which represents metastatic tumour.
 - Epistaxis, nasal obstruction and pharyngeal pain may be present.
 - The tumour may invade through the foramen lacerum into the brain, producing central nervous system (CNS) symptoms or it may involve cranial nerves in the area; causing specific symptoms related to those nerves.

Histopathology

- Nasopharyngeal carcinoma typically shows one of the three histopathologic patterns:
 1. Squamous cell carcinoma (keratinizing squamous cell carcinoma)
 2. Differentiated nonkeratinizing carcinoma (nonkeratinizing squamous cell carcinoma)
 3. Undifferentiated nonkeratinizing carcinoma (poorly differentiated carcinoma, anaplastic carcinoma, lymphoepithelioma)
- The histopathologic features of keratinizing squamous cell carcinoma are identical to those of squamous cell carcinoma of other head and neck regions.

https://t.me/RoyalDentistryLibrary/

- The lesional cells of differentiated nonkeratinizing carcinoma are relatively mature and somewhat squamous in nature, but they produce no keratin.
- Undifferentiated nonkeratinizing carcinoma consists of sheets of lesional cells with less distinct margins that show virtually no differentiation in most instances. These have little cytoplasm and large vesicular nuclei. These tumour cells are often intermixed with the lymphoid cells, normally found at this anatomic site.

Prognosis and predictive factors

- Because of the inaccessibility of the nasopharynx and the high frequency of metastasis at diagnosis, nasopharyngeal carcinoma is treated most frequently with radiotherapy to the nasopharynx and neck. This may be combined with chemotherapy.
- The prognosis ranges from good to poor, depending on the stage of the disease.

Verrucous carcinoma

(Synonym: Ackerman's tumour)

Definition

It is a warty variant of squamous cell carcinoma characterized by a predominantly exophytic overgrowth of well-differentiated keratinizing epithelium having minimal atypia and with locally destructive pushing margins at its interface with underlying connective tissue.

Pathogenesis

- The exact aetiology is unknown.
- Verrucous carcinoma arises from the oral mucosa in people who chronically use chewing tobacco or snuff, typically in the area where the tobacco is habitually placed.
- Human papilloma virus subtypes 16 and 18.

Clinical features

- **Age.** 60–70 years.
- **Gender.** Male predilection.

https://t.me/RoyalDentistryLibrary/

- **Location.** Buccal mucosa, gingiva, alveolar ridge, palate and floor of the mouth.
- **Signs and symptoms**
 - The neoplasm is chiefly exophytic and appears papillary in nature, with a pebbly surface which is sometimes covered by a white leukoplakic film.
 - The lesion commonly has rugae-like folds with deep clefts between them.
 - Lesions on the mandibular ridge or gingiva grow into the overlying soft tissue and rapidly become fixed to the periosteum, gradually invading and destroying the mandible.
 - Regional lymph nodes often tender and enlarge, simulating metastatic tumour, but this node involvement is usually inflammatory.
 - Pain and difficulty in mastication are common complaints, but bleeding is rare.

Histopathology

- Generally, marked epithelial proliferation with down growth of epithelium into connective tissue but usually without a pattern of true invasion.
- The epithelium is well differentiated and shows little mitotic activity, pleomorphism or hyperchromatism.
- Characteristically, cleft-like spaces lined by a thick layer of parakeratin extend from the surface deep into the lesion.
- Parakeratin plugging also occurs extending into the epithelium.
- The basement membrane will often appear intact.
- Chronic inflammatory cell infiltration in the underlying connective tissue may or may not be present.

Prognosis and predictive factors

- Because metastasis is an extremely rare event in verrucous carcinoma, the treatment of choice is surgical excision without radical neck dissection.
- Radiotherapy is effective.
- Chemotherapy may temporarily reduce the size of verrucous carcinoma, but it is not a definitive treatment.

Basal cell carcinoma

(Synonym: Rodent ulcer)

https://t.me/RoyalDentistryLibrary/

Basal cell carcinoma is a locally invasive, slowly spreading primary epithelial malignancy that arises from the basal cell layer of the skin and its appendages.

Pathogenesis

Cancer results from chronic exposure to ultraviolet radiation.

Clinical features

- **Age.** >40 years.
- **Gender.** Male predilection.
- **Location.** Radiation exposed areas of the body.
- **Signs and symptoms**
 - The basal cell carcinoma begins as a firm, painless papule that slowly enlarges and gradually develops a central depression and an umbilicated appearance.
 - One or more telangiectatic blood vessels are usually seen coursing over the rolled border surrounding the central depression. When the lesion is pressed, a characteristic pearly opalescent quality is discerned.
 - Untreated lesions continue to enlarge slowly over months or years, with ulceration and destruction of underlying structure, hence called *rodent ulcer*.
 - Destruction of underlying bone or cartilage may occur, but metastasis is extremely rare.

Histopathology

- It is characterized by neoplastic proliferation of basaloid epithelial cells in the form of multiple solid islands or strands.
- These cells arise from the basal cell layer of epithelium and they invade into the underlying connective tissue.
- The cells in the periphery of the tumour islands are columnar in shape with palisaded arrangement, hyperchromatic nuclei and do not show any abnormal mitosis.
- The central cells of the tumour islands may be polyhedral, oval, round or even spindle shaped.
- Sometimes, these neoplastic cells may show adenoid or cystic growth patterns and squamous metaplasia.

https://t.me/RoyalDentistryLibrary/

Prognosis and predictive factors

- Surgical excision or electrocautery along with radiotherapy is the treatment of choice.
- Recurrence is rare.

Melanoma

Melanoma is a malignant neoplasm of melanocytic origin that arises from a benign melanocytic lesion or de novo from melanocytes within otherwise normal skin or mucosa.

Pathogenesis

- **Environmental factors**
 - Sun exposure
 - Long period of high UV sunlight exposure in childhood
 - Intermittent exposure is more detrimental
 - Artificial UV sources: PUVA (combination of psoralen [P] and long wave ultraviolet radiation [UVA]) therapy, tanning lamp.
 - Socioeconomic status: High socioeconomic status is more prevalent because of holidays trips, outdoor hobbies like sailing.
 - Fair skin, freckles and red hair.
 - Number of melanocytic naevi: Total number of melanocytic naevi, dysplastic or bland are strong risk factors.
- **Genetic factors**
 - Familial melanoma: 2–5% patients have family history.
 - Xeroderma pigmentation: Defective DNA repair mechanism lead to excessive chronic UV damage and development of different sun-related skin tumours.
 - Genes implicated in the development of melanoma includes CDKN2A (P16), CDK4 (chromosome 12q15), RB1, CDKN2A (P19), PTEN/MMAC1 and ras.

Clinical features

- **Age.** 50–55 years.
- Four clinicopathologic types of melanoma have been described:
 1. Superficial spreading melanoma
 2. Nodular melanoma

https://t.me/RoyalDentistryLibrary/

3. Lentigo maligna melanoma
4. Acral lentiginous melanoma

- Melanomas tend to exhibit two directional patterns of growth:
 1. Radial growth phase
 2. Vertical growth phase
- In early stages of melanoma development, the radial growth phase tends to predominate in lentigo maligna melanoma, superficial spreading melanoma and acral lentiginous melanoma.
- In these lesions, the malignant melanocytes tend to spread horizontally through the basal layer of the epidermis.
- Eventually, however, the malignant cells begin to invade the underlying connective tissue, thus initiating the vertical growth phase.
- With nodular melanoma, the radial growth phase is short or nonexistent and the vertical growth phase predominates.

Superficial spreading melanoma

- Most common form of melanoma.
- The common site of origin is the intercapsular area of males and the back of the legs of the females.
- The lesion is smaller than 3 cm in diameter and slightly elevated.
- Clinically, invasion is indicated by the appearance of surface nodules or induration and usually occurs within 1 year of discovery of the precursor macule.

Nodular melanoma

- Common sites are head and neck areas.
- Nodular melanoma is usually a deep pigmented exophytic lesion, sometimes the melanoma cells are so poorly differentiated that they no longer can produce melanin, resulting in a nonpigmented amelanotic melanoma.

Lentigo maligna melanoma

- Common sites are the sun-exposed areas, particularly in the mid-facial region.
- The lesion appears as a large, slowly expanding macule with irregular borders and a variety of colours including tan, brown, black and even white.

- The appearance of nodularity within a lentigo maligna signals the onset of the invasive or vertical growth phase and transition to lentigo maligna melanoma.

Acral lentiginous melanoma

- Most common form of oral melanoma.
- Often occurs in sixth or seventh decade of life and men are frequently affected.
- Common sites are the palms of the hand, soles of feet, subungual area and mucous membrane.
- It begins as darkly pigmented, irregularly marginated macule, which later develops a nodular invasive growth phase.
- An oral lesion typically begins as brown to black macule with irregular borders.
- The macule extends laterally and a lobulated, exophytic mass develops, once the vertical growth is initiated.
- Ulceration may also occur.
- Pain is not a common feature expect in ulcerated lesion. Most lesions remain relatively soft to palpation.

Note: ABCDE rule for clinical diagnosis of melanoma
Asymmetry: One half does not match the other half because of its uncontrolled growth pattern.
Border irregularity with blurred, notched or ragged edges.
Colour irregularity: Pigmentation is not uniform: Brown, black, tan, red, white and blue depending on amount and depth of melanin pigmentation.
Diameter will be greater than 6 mm.
Elevation: A raised surface.

Histopathology

- Malignant cells often nest or cluster in groups in an organoid fashion.
- Melanoma cells: Large nuclei with prominent nucleoli and show nuclear pseudoinclusions due to nuclear membrane irregularity. Cytoplasm is abundant, may be uniformly eosinophilic or optically clear. Occasionally,

cells will become spindle-shaped than round or polygonal cell variants.

Superficial spreading melanoma

- Radial growth phase is characterized by the presence of large epithelioid melanocyte distributed in *pagetoid manner.* This pagetoid spread within epidermis is called as *buckshot scatter.*
- Malignant cells are confined to epithelium—no host cell response in connective tissue.
- When melanocytes penetrate basement membrane, host cell response of lymphocytes develops.
- Macrophages and melanophages may be present.
- Vertical growth phase characterized by proliferation of malignant epithelioid melanocytes in the underlying connective tissue.
- Cells may be arranged singly or in clusters.
- Melanin pigment is usually scanty.

Nodular melanoma

- It is characterized by large epithelioid melanocytes within the connective tissue.
- Small ovoid and spindle-shaped cells may be present.
- Melanin pigment is usually present.
- The tumour cells may invade and ulcerate the overlying epithelium and penetrate deep soft tissues.

Lentigo maligna melanoma

- It is characterized by increased numbers of atypical melanocytes within the basal epithelial layer.
- Epithelium is atrophic generally and the dermal collagen shows the effect of sun damage (basophilic degeneration).
- Cords and nests of atypical melanocytes may be evident.
- Invasive spindle-shaped cells into underlying dermis is seen.
- Lymphohistiocytic infiltrate is present.

Acral lentiginous melanoma

- Similar to lentigo maligna.
- Coleman and his coworkers pointed following features:
 - A lentiginous radial growth phase
 - A deep vertical growth phase composed predominantly of spindle-shaped cells
 - Psoriasiform epidermal hyperplasia
 - An intense host cell response
 - A prominent desmoplasia associated with vertical growth phase

Classification

Clark's classification

Clark's classification of melanoma is given in Table 2.3.

Table 2.3

Clark's classification of melanoma

Level of tumour invasion	Clark's classification
Cells confined to epithelium and are entirely above basement membrane	Level I
Cells penetrating papillary dermis and tumour is still in radial growth phase	Level II
Cells filling papillary dermis throughout and tumour has entered vertical growth phase	Level III
Cells extending into reticular dermis and tumour is seen between collagen bundles	Level IV
Cells invading into subcutaneous fat	Level V

Breslow's classification

Breslow's classification of melanoma is given in Table 2.4.

Table 2.4

Breslow's classification of melanoma

Tumour thickness (mm)	Breslow's classification
0.0–0.75	Low risk
0.76–1.49	Low to intermediate risk
1.5–2.49	Intermediate risk
2.5–3.99	Intermediate to high risk
≥4	High risk

Note: Total tumour thickness as measured from the outermost layer of stratum granulosum to deepest identifiable point of tumour invasion in the dermis.

Prognosis and predictive factors

- Surgical excision is the only curative treatment, although the extent of the excision is somewhat controversial.
- Older literature suggests that surgical margins of 3–5 cm around the tumour are necessary to achieve control, but recent studies indicated that 1 cm margin is adequate for small early tumours.
- Surgical removal of regional lymph nodes is recommended for lesion with histopathologic depth of invasion that exceeds 1.24 mm.
- Radiation therapy has no significant impact on survival, although adjunct chemotherapy and immunotherapy are showing promise.

Benign tumours of connective tissue origin

Oral fibromatous lesions/fibroma/giant cell fibroma

Oral fibromatous lesions include the connective tissue lesions such as oral fibroma and fibromatoses. It can be further classified into: (i) predominantly fibrous tumours, (ii) reactive hyperplasia and (iii) intermediate tumours like fibromatoses.

Fibroma

(Synonyms: Irritation fibroma; traumatic fibroma; focal fibrous hyperplasia; fibrous nodule)

- It is the most common benign soft tissue tumour of connective tissue origin in the oral cavity.
- Most of the fibromas represent the focal fibrous hyperplasia in response to the local irritation or trauma.
- It is not a true neoplasm since it ceases to grow once it reaches about 2 cm in diameter.

Clinical features

- **Age.** 20–40 years.
- **Gender.** Female predilection.
- **Location.** Buccal mucosa along the plane of occlusion, labial mucosa, tongue and gingiva.
- **Signs and symptoms**
 - Fibroma is a slow-growing lesion which appears as an elevated smooth-surfaced pink nodule with a sessile or occasionally pedunculated base.
 - The size ranges between few millimetres to about several centimetres.
 - In some cases, the surface may be ulcerated or hyperkeratotic due to continued irritation of the mucosa projecting above the surface.

Histopathology

- It shows a nodular fibrous connective tissue covered by a stratified squamous epithelium, which shows shortening and flattening of the rete ridges (epithelial atrophy).
- The connective tissue consists of bundles of collagenous fibres interspersed with varying number of fibroblasts or fibrocytes and small

blood vessels. The collagen bundles may be arranged in a radiating, circular or haphazard fashion.
- Secondary inflammation mostly of chronic nature may be seen beneath the epithelial surface.
- Areas of diffuse calcification or ossifications may also be seen.
- Sometimes, an untreated pyogenic granuloma can undergo healing by sclerosis and may mimic fibroma microscopically.

Prognosis and predictive factors

- Conservative surgical excision can be done and the lesion seldom recurs.

Giant cell fibroma

- Giant cell fibroma is a fibrous tumour with distinctive clinicopathologic features.
- It is not associated with chronic irritation and its distinctive histopathologic pattern differentiates it from the conventional fibroma.

Clinical features

- **Age.** 10–30 years.
- **Gender.** Female predilection.
- **Location.** Mandibular gingiva followed by maxillary gingiva, tongue and the palate.
- **Signs and symptoms.** It appears as an asymptomatic sessile or pedunculated nodule, usually less than 1 cm in diameter. The surface appears papillary or bosselated and hence can be mistaken to be a papilloma.

Histopathology

- Giant cell fibroma reveals a mass of vascular fibrous connective tissue which is unencapsulated.
- The '*hallmark*' of the lesion is that it presents with large, plump, spindle-shaped and stellate fibroblasts, some of which are multinucleated. These cells are seen in the periphery and central areas and show fusiform fibroblasts.
- The surface epithelium is corrugated and atrophic; the rete ridges are thin and elongated.

Prognosis and predictive factors

- The giant cell fibroma is treated by conservative surgical excision.
- Recurrence is rare.

Peripheral ossifying fibroma

(Synonyms: Ossifying fibroid epulis; calcifying fibroblastic granuloma)
The peripheral ossifying fibroma occurs as a common gingival growth which is reactive in nature.

Pathogenesis

- Uncertain
- Pyogenic granuloma
 ↓
 Fibroma
 ↓
 Peripheral ossifying fibroma
- Mineralized product has its origin from cells of the periosteum or periodontal ligament.

Clinical features

- **Age.** 10–30 years.
- **Gender.** Female predilection.
- **Location.** Maxillary incisor–cuspid region of gingival.
- **Signs and symptoms**
 - Teeth are not affected except that there may be migration and loosening of adjacent teeth.
 - It appears as a nodular mass arising from the interdental papilla which may be either sessile or pedunculated.

Radiographic features

- No apparent underlying bone involvement is seen.
- Rarely superficial erosion of bone is seen.

Histopathology

- Peripheral ossifying fibroma shows a fibrous proliferation associated with formation of mineralized product.

- The overlying epithelium may be ulcerated and sometimes it may be covered by a fibrinopurulent membrane.
- The mineralized content may vary and consist of unmineralized osteoid, ovoid droplets of basophilic cementum-like material, dystrophic calcifications characterized by multiple granules or tiny globules are seen.
- Multinucleated giant cells are also seen.

Prognosis and predictive factors

Local surgical excision of the mass up to the periosteum to prevent recurrence should be done.

Central ossifying fibroma

(Synonym: Central fibro-osteoma)
It is a central neoplasm of bone.

Clinical features

- **Age.** Young adults.
- **Gender.** Female predilection.
- **Location.** Mandible is commonly affected.
- **Signs and symptoms**
 - Asymptomatic, until the growth produces noticeable swelling and mild deformity.
 - Slow-growing swelling which shows cortical plates of bone and overlying mucosa intact.

Radiographic features

- It is well circumscribed and demarcated from surrounding bone, in contrast to fibrous dysplasia.
- In early stages, radiolucent area with no evidence of radiopacities is seen.
- As tumour matures, radiolucent areas become flecked with opacities until the lesion appears as uniform radiopaque mass.
- Displacement of adjacent teeth is seen.

Histopathology

- Delicate interlacing collagen fibres seldom arranged in discrete bundles, interspersed by large number of active proliferating fibroblasts.

- As the lesion matures, the islands of ossification increase in number, enlarge and ultimately coalesce.

Prognosis and predictive factors

The lesion should be excised conservatively and recurrence is rare.

Peripheral giant cell granuloma

(Synonyms: Peripheral giant cell epulis; peripheral giant cell reparative granuloma)

- Peripheral giant cell granuloma is a tumour-like growth which does not represent a true neoplasm.
- It is a reactive lesion caused by local irritation or trauma, hence previously it was called as *reparative granuloma*.

Pathogenesis

- The exact aetiology is unknown.
- Local irritation due to dental plaque or calculus.
- Periodontal disease.
- Poor dental restorations.
- Ill-fitting dental appliances.
- Dental extractions.

The giant cells seen in peripheral giant cell granuloma resemble osteoclasts and mostly are derived from the mononuclear phagocyte system.

Clinical features

- **Age.** 31–41 years.
- **Gender.** Female predilection.
- **Location.** Mandible is commonly affected. The most common site of occurrence is gingiva or alveolar mucosa of edentulous ridges.
- **Signs and symptoms**
 - It presents as a red or red-blue nodular mass.
 - The lesion presents as a nodular mass less than 2 cm in diameter and can be sessile or pedunculated.
 - It occurs within the soft tissue, but *cupping resorption* of the underlying bone may be seen.

Histopathology

- It shows proliferation of multinucleated giant cells within a background of plump ovoid and spindle-shaped mesenchymal cells.
- The giant cells may contain few to several nuclei; these can be large vesicular nuclei or may show pyknotic nuclei.
- There is a separation of fibrous connective tissue from the giant cell proliferation.
- Areas of reactive bone formation or dystrophic calcification along with mixed inflammatory cell infiltrate are seen.
- The overlying surface is mostly ulcerated.

Prognosis and predictive factors

- Local surgical excision down to the underlying bone should be done.
- The adjacent teeth should be removed of any irritation to minimize the risk of occurrence.

Central giant cell granuloma

(Synonym: Giant cell tumour of bone)
These lesions were found to be destructive rather than reparative, hence the word reparative was omitted from that term.

Clinical features

- **Age.** 2–80 years.
- **Gender.** Female predilection.
- **Location.** Mandible is commonly affected. The most common site of occurrence is anterior portions of jaws.
- **Signs and symptoms**
 - Asymptomatic, hence it is identified during routine radiographic examination or painless expansion of bone.
 - In few cases, pain, paraesthesia or perforation of cortical bone plate is seen.
 - Based on clinical and radiographic features, central giant cell granulomas may be divided into two categories:
 1. *Non-aggressive lesions*
 – Most cases exhibit few or no symptoms.
 – Slow growth.

– These do not show cortical perforation or root resorption of teeth.

2. *Aggressive lesions*
 – Painful and rapid growth.
 – Cortical perforation and root resorption are seen.
 – Tendency to recur after treatment.

Radiographic features

- Unilocular or multilocular radiolucency is seen.
- Defect is delineated but margins are noncorticated.

Histopathology

- Few to many multinucleated giant cells in a background of ovoid to spindle-shaped mesenchymal cells and macrophages are seen.
- Giant cells may aggravate focally in the lesional tissue or diffusely throughout the lesion.
- Giant cells may vary in size and shape:
 - Small and irregular in shape and contain only few nuclei.
 - Large and round in shape and contain 20 or more nuclei.
- Stroma is loosely arranged and oedematous or cellular.
- Areas of haemorrhage and haemosiderin deposition are prominent.
- Foci of osteoid and newly formed bone are occasionally present.

Prognosis and predictive factors

The treatment of the giant cell granuloma is curettage or surgical excision.

Lipoma

The lipoma is a benign tumour of fat tissue.

Pathogenesis

- The *HMGI-C* gene, which has been mapped to 12q15, is a member of high mobility group protein gene family and plays an important role in lipoma development.
- The cells of the lipoma differ metabolically from normal fat cells. Fatty acid precursors are incorporated at a faster rate into lipoma fat than into normal fat while lipoprotein lipase activity is reduced.

Clinical features

- **Age.** It usually occurs among adults.
- **Gender.** No sex predilection.
- **Location.** Tongue, floor of the mouth, buccal mucosa and mucobuccal folds.
- **Signs and symptoms**
 - The size of the lesion ranges from 3 cm at the time of diagnosis to 5–6 cm over a period of years.
 - Morphologically, intraoral lipomas are classified as:
 - Superficial and encapsulated form
 - Diffuse form affecting the deeper tissues
 - *Superficial form* appears as a yellowish single, lobulated, painless lesion with a sessile or pedunculated base.
 - *Diffuse form* feels like fluid. It occurs in areas where fat is normally present and the diagnosis depends on the overabundance of the tissue.
 - Multiple lipomas are seen in neurofibromatosis, Gardener's syndrome, encephalo-cranio-cutaneous lipomatosis, multiple familial lipomatosis and proteus syndrome.

Histopathology (fig. 2.4)

- It consists of lobular arrangement of adipocytes and is separated from the adjacent connective tissues by a fibrous capsule.
- Microscopic variants:
 - *Fibrolipoma:* Fibrous component intermixed with lobules of fat cells.
 - *Angiolipoma:* Admixture of mature fat and numerous small blood vessels.
 - *Spindle cell lipoma:* Variable amounts of spindle cells in conjunction with lipomatous component. When it is associated with a myxoid background, it is described as *myxoid lipoma*.
 - *Pleomorphic lipomas:* Spindle cells plus bizarre, hyperchromatic giant cells.
 - *Intramuscular lipomas:* Deeply situated and has infiltrative growth that extends between skeletal muscle bundles.

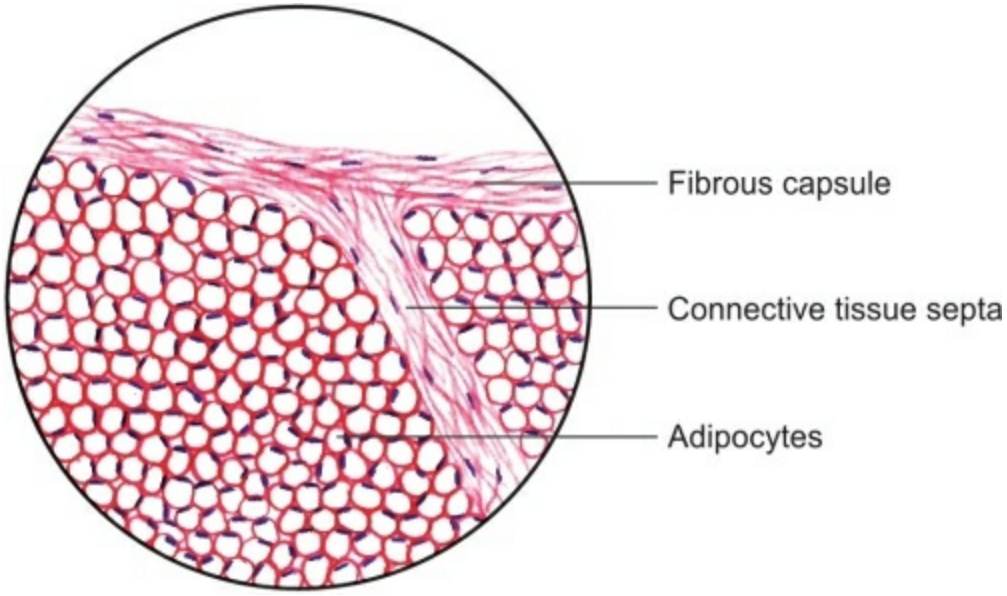


FIG. 2.4 Lipoma.

Prognosis and predictive factors

- Treatment is by conservative local excision.
- Microscopic variants do not affect the prognosis.

Haemangioma

Haemangiomas are tumour-like malformations (hamartomas) composed of seemingly disorganized masses of endothelium-lined vessels that are filled with blood and connected to the main blood vascular system.

Types of haemangioma

- Capillary haemangioma
- Cavernous haemangioma
- Naevus flammeus/port-wine haemangioma
- Intramuscular haemangiomas
- Central haemangioma of bone

Syndromes associated with haemangiomas

- Rendu–Osler–Weber syndrome
- Sturge–Weber syndrome
- Kasabach–Merritt syndrome
- Maffucci's syndrome

- von Hippel–Lindau syndrome
- Klippel–Trenaunay syndrome

Clinical features

- **Age.** Most haemangiomas are evident at birth and they frequently increase in size with general bodily growth and regress at puberty.
- **Site**
 - The most common oral sites are the tongue and the lip.
 - These have been described in almost all locations in and about the oral cavity and face and may involve deep structures such as the jaw and facial bones, salivary glands, muscles and the temporomandibular joint, as well as the surface mucosa and skin.
- **Gender.** Female predilection.
- **Signs and symptoms**
 - Depending on the depth of the vascular proliferation within the oral submucosa, the lesion may harbour vessels close to the overlying epithelium and appear reddish blue or, if a little deeper in the connective tissue, a deep blue.
 - Large lesions are warm and may even be pulsatile, if associated with a large blood vessel.
 - Haemodynamics is perturbed and stasis with thrombosis is common. When thrombi calcify, the lesions are hard on palpation.

Capillary haemangioma

- It consists of masses of proliferating vessels of capillary dimension. Due to their bright red colour, they have been referred to as *strawberry haemangiomas*.
- Lesion begins as a flat area of red pigmentation that is noted at birth or during the first few weeks of life. It rapidly proliferates over the next 6–12 months and produces an elevated and lobulated mass that is red to purple colour.
- By 7 years of age, most of the haemangiomas involute.
- These lesions bleed profusely, when traumatized.

Cavernous haemangioma

- It consists of large blood-filled lakes.
- The lesions are less circumscribed and more frequently involve deeper

structures.
- Bleed profusely when traumatized.

Port-wine haemangioma

- It is flat, macular and diffuse, magenta red in colour particularly on the facial skin.
- The port-wine haemangioma of facial skin may concomitantly involve the oral mucosa, where the angioma may continue in macular fashion or become tumefactive.

Intramuscular haemangioma

- Angiomatous lesions occurring within muscle may fail to show any surface discolouration.
- Intraorally, these may occur deeply within the intrinsic muscles of the tongue.
- Sometimes, these are not clinically visible.

Central haemangioma

- It is a bone destructive lesion which may be of varying size and appearance.
- More common in the mandible than in the maxilla.
- Mobility of teeth or bleeding from the gingival sulcus is common.
- Root resorption of the involved teeth is seen.
- Severe haemorrhage following dental extractions is seen.
- Expansion of the alveolar process with diminished depth of the mucobuccal fold.
- On aspiration, they yield blood readily.

Radiographic features

On a conventional radiograph, central haemangiomas can appear as:

- Multilocular radiolucent defect—honeycomb pattern.
- Unilocular well-defined cyst-like radiolucency.
- Sunburst radiographic pattern.
- Presence of phleboliths or a wavy doughnut-shaped radiopacity represents a large calcified blood vessel wall.
- Displacement of teeth and root resorption are seen.
- When associated with Sturge–Weber syndrome, tramline-like

calcifications is seen.

Histopathology

- Early haemangiomas show numerous plump endothelial cells and often indistinct vascular lumina.
- With maturation, the endothelial cells become flattened and the small capillary-sized vascular spaces become more evident.
- As the haemangioma undergoes involution, the vascular spaces become more dilated and widely spaced.
- Cavernous form of haemangioma consists of large dilated blood sinuses (spaces) with thin walls, each showing an endothelial lining. The sinusoidal spaces are usually filled with blood (Fig. 2.5).

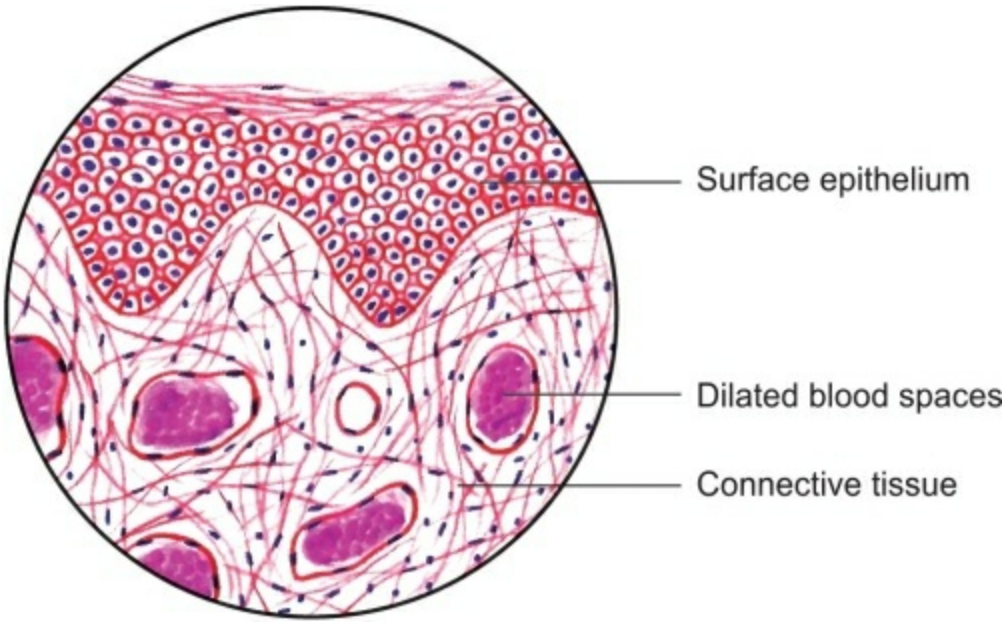


FIG. 2.5 Cavernous haemangioma.

Prognosis and predictive factors

- *Medical management*
 - Corticosteroids: 20–40 mg/dl of prednisone for 30–90 days and then taper the drug
 - Interferon alpha
- Sclerotherapy involves the injection of sclerosing agents such as 95% ethanol, directly into the lesion to induce fibrosis. Sclerotherapy alone

may be sufficient for smaller lesions; for larger lesions, subsequent surgical resection can be accomplished with less risk of bleeding after sclerotherapy.

- *Conventional surgery:* Complete excision of the lesion is curative, but if conventional surgery is being replaced by cryosurgery, there is fear of uncontrolled haemorrhage in conventional surgery. In general, electrocoagulation and cryosurgery cause less postoperative haemorrhage than incision with a scalpel causes.
- *Cryosurgery:* Cryosurgery for cutaneous lesions has been associated with scarring, but there is good haemostasis.
- *Embolization:* Embolization means the occlusion of a vessel by the introduction of a foreign body that helps to shrink the size of the lesion, e.g. silastic spheres, acrylic spheres.
- Flashlamp pulsed dye lasers can be effective in the treatment of port-wine stains.

Vascular malformations

Vascular malformations are structural anomalies of blood vessels without endothelial proliferation. These are present at birth and persist throughout life. They are categorized according to the type of vessel involved (capillary, venous, arteriovenous) and according to haemodynamic features (low flow or high flow).

Hereditary haemorrhagic telangiectasia

(Synonyms: Rendu–Osler–Weber syndrome; hereditary familial angiomatosis; familial haemorrhagic angiomatosis)

- Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant disorder.
- It includes triad of telangiectasia, recurrent epistaxis and positive family history.
- It is the major cause of morbidity and mortality due to the presence of multiorgan arterio- venous (AV) malformations with associated haemorrhage.

Pathogenesis

- Mutation of either one of the two different genes at two separate loci is responsible for the condition.

- HHT1 is caused by a mutation of the *ENG* (endoglin) gene located on chromosome 9q33-q34.
- HHT2 is caused by a mutation of the *ALK1* (activin receptor-like kinase 1) gene located on chromosome 12.
- The proteins produced by these genes may play a role in blood vessel wall integrity.

Clinical features

- **Age.** Occasionally present at or shortly after birth, but mostly do not become conspicuous.
- **Gender.** No sex predilection.
- **Location**
 - Skin over the face, neck and chest.
 - In oral cavity: Lips, gingiva, buccal mucosa, palate, floor of the mouth and tongue.
- **Signs and symptoms**
 - Earliest signs: Epistaxis as well as bleeding from the oral cavity.
 - The nasal and oropharyngeal mucosae exhibit numerous scattered red papules 1–2 mm in size, which blanches. This blanching indicates that red colour is due to the blood contained within blood vessels.
 - Spider-like telangiectasis is seen on vermilion zone of lips, tongue and buccal mucosa, which increases in number and prominences as age advances.

Histopathology

A superficially located collection of thin-walled vascular spaces that contain RBCs is seen.

Prognosis and predictive factors

- Treatment depends on the severity.
- Spontaneous haemorrhages are controlled by pressure packs.
- Telangiectatic areas are sometimes cauterized or surgically excised.

Sturge–Weber syndrome

(Synonym: Encephalotrigeminal haemangiomatosis)

It is a rare nonhereditary developmental condition, characterized by a hamartomatous vascular proliferation involving tissues of brain and face.

Pathogenesis

- The primary defect is a developmental insult affecting precursors of tissues that originate in the promesencephalic and mesencephalic neural crests. Then, these affected precursors give rise to vascular and other tissue malformations in the meninges, eye and dermis.
- No gene defect has been associated with the syndrome.

Clinical features

- *Port-wine stain* or *naevus flammeus* has a unilateral distribution along one or more segments of trigeminal nerve.
- *Leptomeningeal angiomas* that overly the ipsilateral cerebral cortex, associated with a convulsive disorder and often result in mental retardation or contralateral hemiplegia.
- *Ocular manifestations:* Glaucoma, vascular manifestation of conjunctiva, choroid and retina.
- *Oral manifestations*
 - Hypervascular changes to the ipsilateral mucosa is seen.
 - Gingival hyperplasia: Due to the increased vascular component, phenytoin therapy is used to control epileptic seizures.
 - Rarely destruction of underlying alveolar bone.

Radiological features

Skull radiography reveals vessel wall calcification that yields bilamellar radiopaque tracks—gyriform *tramline* calcifications.

Histopathology

- Excessive numbers of dilated blood vessels in the middle and deep dermis.
- The intraoral lesions show a similar vascular dilation.

Prognosis and predictive factors

- Anticonvulsant medications.
- Laser therapy.
- During oral prophylaxis, precautions must be taken as severe haemorrhage may be encountered.

Lymphangioma

The lymphangioma is a benign hamartomatous hyperplasia of lymphatic vessels.

Pathogenesis

It is thought to be developmental malformation of vessels which has poor communication with normal lymphatic system.

Classification (Watson and Mccarthy, 1940)

- Simple lymphangioma
- Cavernous lymphangioma
- Cellular or hypertrophic lymphangioma
- Diffuse systemic lymphangioma
- Cystic lymphangioma (cystic hygroma)

Clinical features

- **Age.** It usually presents at birth or before the age of 10 years.
- **Gender.** No sex predilection.
- **Location**
 - It is most common in head and neck regions—lateral portion of neck.
 - Intraoral site: Tongue, palate, buccal mucosa, gingiva and lips.
- **Signs and symptoms**
 - In lateral portion of neck, lesions typically contains large cystic spaces —*cystic lymphangioma* or *cystic hygroma*.
 - Tongue involvement: Anterior dorsal part of tongue is frequently affected. The irregular nodularity of the surface with grey and pink projections is associated with enlargement of the tongue (macroglossia) which is pathognomonic.
 - Lip involvement: Macrocheilia.
 - *Superficial lesions:* Papillary lesions which may be of the similar colour as surrounding mucosa or slightly reddened.
 - *Deeper lesions:* Diffuse nodules or masses without any significant change in surface texture or colour.

Histopathology

- Lymphangioma shows numerous interlaced lymphatic channels and the cavernous type presents with dilated lymphatics lined with a single layer of endothelial cells and contain lymph.

- Lymphatic channels rarely may be filled with blood, when it is called as mixed hemangiolymphangioma.
- In oral lymphangiomas, the lymph vessels may be located immediately beneath the epithelial surface and thus many a times replace the connective tissue papilla.
- Cystic hygromas usually present with large interlacing endothelial lined cyst-like spaces.

Prognosis and predictive factors

- Surgical excision is the most preferred treatment though the total removal may not be possible in all cases due to its size.
- Recurrence is more common with cavernous lymphangioma of the oral cavity.
- Prognosis is good except for large lesions of the neck or tongue which can result in airway obstruction and death.

Chondroma

- A chondroma is a benign cartilaginous tumour, which is encapsulated with a lobular growing pattern.
- The lesion is of clinical importance because of the propensity of tumour to undergo malignant degeneration.

Clinical features

- **Age.** It occurs at any age group.
- **Gender.** No sex predilection.
- **Location**
 - Maxilla: Anterior portion, where vestigial cartilage rests are found—midline lingual to or between the central incisors.
 - Mandible: Posterior to cuspid tooth, involving the body of the mandible or coronoid or condylar process.
 - Nasal septum and nasal spine.
- **Signs and symptoms**
 - It is a slow-growing painless swelling of the jaw, which may cause loosening of the tooth and root resorption occasionally.
 - The overlying mucosa is seldom ulcerated.

Radiographic features

- It appears as irregular radiolucency or mottled area in the bone.
- Chondroma is a destructive lesion and causes root resorption of teeth adjacent to it.
- Discrete, irregular, ring-like or curvilinear calcifications are often demonstrable.
- Multiple widespread involvement with unilateral tendency is termed as *Ollier's disease.*
- Skeletal chondromatosis associated with soft tissue angiomas is referred to as *Maffucci's syndrome.*

Histopathology

- It consists of mature hyaline cartilage with small chondrocytes that have pale cytoplasm and round small nuclei.
- In most of the cases, mature or fairly mature hyaline cartilages are arranged in a distinct lobular pattern with sharp borders.
- Some of the tumours are altered by:
 - Focal fibrosis: Fibrochondroma
 - Ossification: Osteochondroma
 - Myxoid change: Myxochondroma
- Some cases display focal or diffuse calcifications. The calcified material is granular, floccular or crystalline and often outlines the contours of the chondrocytes in a lace-like pattern.
- Calcification tends to be more pronounced in centre than at the periphery of the tumour lobule.

Prognosis and predictive factors

- Treatment is directed towards surgical removal of the lesion.
- Condylar tumours are managed by condylectomy.

Osteoma, osteoblastoma (giant osteoid osteoma) and osteoid osteoma

- Osteomasare benign tumours composed of mature compact or cancellous bone and are restricted to craniofacial skeleton.
- Osteoblastoma is a benign neoplasm of bone arising from osteoblasts closely resembles cementoblastoma clinically.
- Osteoid osteoma is a benign bone tumour that shares similar histopathological features of osteoma but differs from osteoblastoma in

its tumour nidus.

Clinical features

Osteoma

- **Age.** Young adults.
- **Gender.** No gender predilection.
- **Location.** Body of the mandible posterior to premolars on the lingual surface, condyle, angle, coronoid and ramus.
- **Signs and symptoms**
 - It arises as polypoid or sessile mass (periosteal osteoma) or located in medullary bone (endosteal osteoma).
 - Osteoma of the condyle shifts the patient's occlusion causing deviation of midline to the unaffected side.
 - Multiple osteomas of the jaws, long bones and skull are characteristic features of *Gardener's syndrome.*

Osteoblastoma

- **Age.** <30 years.
- **Gender.** Male predilection.
- **Location.** Vertebral column, axilla and mandible.
- **Signs and symptoms**
 - Lesion is characterized by pain and swelling at the tumour site.
 - Pain is more generalized and less likely to be relieved by salicylates.

Osteoid osteoma

- **Age.** <10 years.
- **Gender.** Male predilection.
- **Location.** Femur, tibia and phalanges. Mandible is commonly involved.
- **Signs and symptoms**
 - Chief symptom being severe unrelenting and sharp pain that aggravates at night and is relieved by aspirin.
 - Localized swelling of the soft tissue over the involved area of bone may occur and may be tender.

Radiographic features

- *Osteoma:* Well-circumscribed radiopaque mass indistinguishable from scar bone.

- *Osteoblastoma:* Well-defined radiolucent lesion with patchy areas of mineralization.
- *Osteoid osteoma:* Well-circumscribed radiolucent defect usually less than 1 cm with a surrounding zone of reactive sclerosis. Small radiopaque nidus may be present.

Histopathology

Osteoma

- Normal appearing dense bone with minimal marrow tissue is seen in compact osteomas.
- Cancellous osteoma consists of trabeculae of bone and fibro-fatty marrow.

Osteoblastoma

- Vascularity of the lesion with many dilated capillaries is seen.
- Moderate number of multinucleated giant cells and actively proliferating osteoblasts which pave the irregular trabeculae of new bone.

Osteoid osteoma

- It consists of a central nidus composed of compact osteoid tissue varying in degree of calcification.
- The formation of definite trabeculae lined by osteoblasts is seen.
- Neural staining techniques reveal many axons throughout the lesion which accounts for the pain (nidus).

Prognosis and predictive factors

Surgical excision is the treatment of choice for osteoma, osteoblastoma and osteoid osteomas with very less recurrence rate.

Leiomyoma

- It is a benign tumour derived from smooth muscle.
- Most of them are seen as fibroids in the uterus.
- It is rare in oral cavity because of absence of smooth muscle except in blood vessel walls and in circumvallate papillae of tongue.

Types of leiomyoma

There are three types of leiomyoma:

1. Solid leiomyoma
2. Vascular leiomyoma (angiomyoma or angioleiomyoma)
3. Epithelioid leiomyoma (leiomyoblastoma)
 - Solid and vascular leiomyomas are common in oral cavity.
 - Epithelioid leiomyoma is rare in oral cavity.

Clinical features

- **Age.** >30 years.
- **Gender.** No sex predilection.
- **Location.** Blood vessel wall and posterior portion of the dorsum of the tongue near the circumvallate papilla, palate, cheeks, gingiva, lips and salivary glands.
- **Signs and symptoms**
 - It is a slow-growing, firm, mucosal nodule which is asymptomatic, occasionally may be painful.
 - Solid leiomyomas are normal in colour.
 - Angiomyomas exhibit bluish hue.

Histopathology

- Solid leiomyomas are well-circumscribed tumours consisting of interlacing bundles of spindle-shaped smooth muscle cells. The nuclei are elongated, pale staining and blunt ended. Mitotic figures are uncommon.
- Angiomyomas are well-circumscribed lesions that demonstrate multiple tortuous blood vessels with thickened walls caused by hyperplasia of their smooth muscle coats. Intertwining bundles of smooth muscle may be found between the vessels, sometimes with intermixed adipose tissue.
- Epithelioid leiomyoma is composed of epithelioid cells rather than spindle cells.
- Special stains, such as Masson's trichrome stains red for smooth muscles and phosphotungstic acid haematoxylin (PTAH), are used to demonstrate myofibrils.
- Immunohistochemistry reveals positivity for vimentin, smooth muscle actin and desmin.

Prognosis and predictive factors

Local surgical excision; recurrence is rare.

Rhabdomyoma

- Rhabdomyoma is defined as benign neoplasm of striated muscle tissue consisting usually of polygonal vacuolated glycogen containing cells with a fine granular deeply acidophilic cytoplasm resembling myofibrils in cut section.
- It is a hamartomatous rather than a true neoplasm.

Types of rhabdomyomas

There are three types of rhabdomyomas:
1. Adult type
2. Fetal type
3. Genital type—very rare

Pathogenesis

Translocation (reciprocal) has been found in chromosomes 15 and 17.

Clinical features

Adult rhabdomyomas

- **Age.** 16–82 years.
- **Gender.** Male predilection.
- **Location**
 - Pharynx, oral cavity and larynx.
 - Oral cavity: Floor of the mouth, soft palate and base of the tongue.

Fetal rhabdomyomas

- **Age.** Newborns and young children.
- **Gender.** Male predilection.
- **Location.** Face and preauricular region.
 - Both tumours appear as a nodule, which grows to larger size before it is noticed.
 - Laryngeal and pharyngeal lesions lead to airway obstruction.

Histopathology

Adult rhabdomyomas

- Well-circumscribed lobules of large polygonal cells exhibiting granular

and eosinophilic cytoplasm.
- Peripheral vacuolization resulting in a spider-web appearance of cytoplasm.

Fetal rhabdomyomas

- The haphazard arrangement of spindle-shaped muscle cells within a myxoid stroma is seen.
- The cellularity of cells and considerable pleomorphism are seen (mistaken for rhabdomyosarcoma).

Prognosis and predictive factors

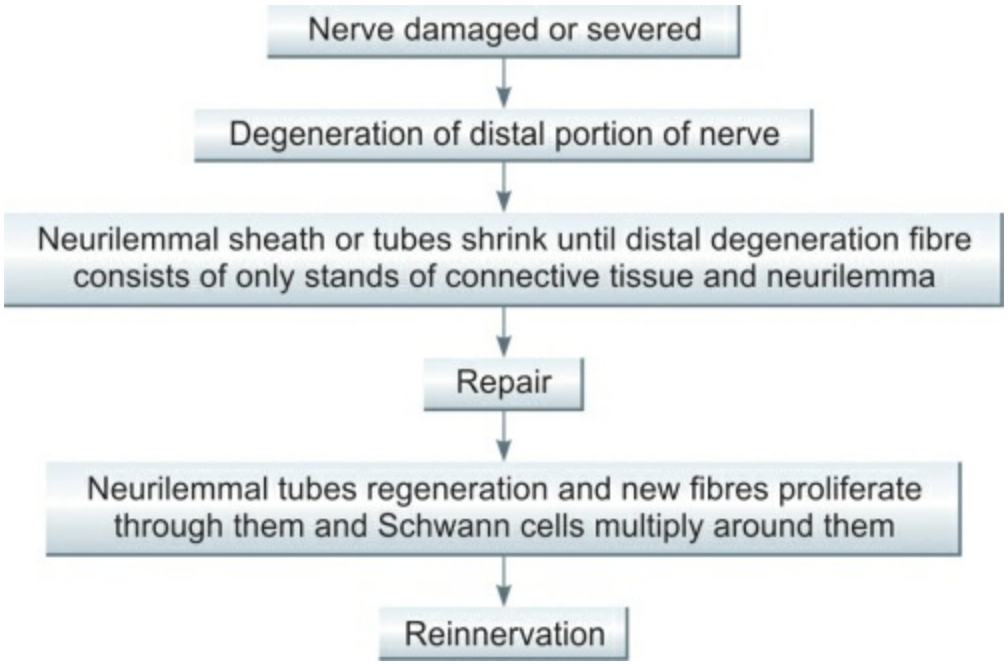
Excision is curative and recurrence is rare.

Traumatic neuroma

It is not a true neoplasm. It is a reactive proliferation of neural tissue after transective or other damage of a nerve bundle.

Pathogenesis

If proliferating proximal end of damaged nerve meets some obstruction such as scar tissue or malaligned bone, nerve continues to proliferate into an unorganized bulbous or nodular mass of nerve fibres and Schwann cells in varying proportions, which forms a *traumatic neuroma* (Flowchart 2.3).



FLOWCHART 2.3 Pathogenesis of traumatic neuroma

Clinical features

- **Age.** Usually middle age group.
- **Gender.** Female predilection.
- **Location.** Mental foramen area, tongue and lower lip.
- **Signs and symptoms**
 - Traumatic neuroma of oral mucosa appears as smooth surfaced, non-ulcerated nodules.
 - Altered nerve sensation is seen.
 - Pain may be intermittent or constant and range from mild tenderness or burning sensation to severe radiating pain.
 - History of trauma often can be elicited like tooth extraction or other surgical procedures.

Histopathology

- Irregular proliferation of mature, myelinated and unmyelinated nerve bundles with fibrous connective tissue stroma that ranges from densely collagenized to myxomatous in nature.
- Mild chronic inflammatory cell infiltrate may be present.
- Proliferating nerve fibres can occur either in small discrete bundles or spread diffusely throughout the tissue.

Prognosis and predictive factors

- Surgical excision is generally advocated.
- Recurrence is uncommon.

Neurofibroma

- It is a peripheral nerve neoplasm.
- It arises from mixture of cell types including Schwann cells and perineural fibroblasts.
- Neurofibroma may assume one of the three growth patterns—(i) localized, (ii) diffuse and (iii) plexiform.

Pathogenesis

- Localized neurofibroma occurs most often as sporadic lesions.
- Diffuse and plexiform neurofibromas have a close association with neurofibromatosis 1 (NF1).

Clinical features

- **Age.** 20–30 years.
- **Gender.** No sex predilection.
- **Location.** Most of the lesions are superficial lesions of the dermis or subcutis, they are found evenly distributed over the body surface.
- **Signs and symptoms**
 - These grow slowly as painless nodules and produce few symptoms.
 - If they arise from major nerves, they expand the structure in a fusiform fashion and normal nerve can be seen entering and exiting from the mass. If such lesions remain confined by the epineurium, it has a true capsule.
 - More commonly, these tumours arise in small nerves and appear circumscribed but are nonencapsulated.

Histopathology

- Histopathologically, it varies depending on its content of cells, mucin and collagen.
- The neurofibroma contains interlacing bundles of elongated cells with wavy, dark staining nuclei representing neural cells and strands of collagen fibres.

- Small to moderate amounts of mucoid material separate the cells and collagen.
- The stroma of the tumour contains mast cells, lymphocytes and rarely xanthoma cells.
- Sometimes, neurofibroma is highly cellular and consists of neural cells in a uniform collagen matrix devoid of mucosubstances. The cells may be arranged in short fascicles, whorls or even a storiform pattern.
- Rarely, tumours are highly myxoid. These hypocellular neoplasms contain pools of acid mucopolysaccharide with widely spaced neural cells.
- *Plexiform neurofibroma:* Distorted masses of myxomatous peripheral nerve tissue still within the perineural sheath are scattered within a collagen-rich matrix.

Prognosis and predictive factors

- Surgical excision.
- Recurrence is uncommon.
- Malignant transformation is common.

Neurofibromatosis

(Synonym: von Recklinghausen disease)

It was first described by von Recklinghausen in 1882. The common forms are:

- *Neurofibromatosis type 1 (NF1):* Peripheral form of neurofibromatosis.
- *Neurofibromatosis type 2 (NF2):* Central form of neurofibromatosis.

Neurofibromatosis type 1

Pathogenesis

- It is inherited as an autosomal dominant trait with a high rate of penetrance.
- It is associated with deletions, insertions or mutations in the *NF1* gene, a tumour suppressor gene located in the pericentromeric region of chromosome 17.
- It encodes a protein known as neurofibrin, which has been localized to various portions of the cells including the microtubular system.
- Although function of neurofibromin is not fully defined, it is homologous to the family GAP proteins (guanosine triphosphate activating protein), which are believed to be important in the central growth through their

downregulation of the *ras* gene.

Clinical findings

Diagnostic criteria for neurofibromatosis type 1
Patient should have two or more features of the following:
1. Six or more café-au-lait macules.
2. Two or more neurofibromas of any type or one plexiform neurofibroma.
3. Freckling in the axillary or inguinal region.
4. Optic glioma.
5. Two or more Lisch nodules (Iris hamartomas).
6. A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis.
7. First degree relative (parent, sibling, off spring) with NF1 by the above criteria.

Oral manifestations

- Enlargement of fungiform papillae.
- Unilateral enlargement of tongue.

Radiographic features

- Enlargement of mandibular foramen.
- Enlargement or branching of mandibular canal.
- Concavity of medial surface of ramus.
- Increase in dimension of coronoid notch.

Neurofibromatosis type 2

Pathogenesis

- It is inherited as an autosomal dominant trait with a high rate of penetrance.
- The *NF2* gene is a tumour suppressor gene located on chromosome 22, which encodes cytoskeleton associated proteins—*merlin* or *schwannomin.*
- NF2 is associated with inactivating mutations of the allele, resulting in the absence of the gene product merlin in the tumours.

Clinical features

- The onset of NF2 is with the development of tinnitus or hearing loss due

to the presence of bilateral acoustic schwannomas, which usually affect the vestibular portion of the eighth cranial nerve.
- Café-au-lait spots and neurofibromas are rare or absent.
- Other CNS tumours occur commonly including schwannomas of other cranial nerves, meningioma, ependymoma and glioma.

Histopathology

- It is composed of a proliferation of delicate spindle cells with thin, wavy nuclei intermingled with neuritis in an irregular pattern as well as delicate, intertwining connective tissue fibrils.
- Melanocytes may sometimes be found in the tumour and mast cells are common.
- The lesions may be well circumscribed.

Prognosis and predictive factors

- There is no specific therapy for NF1 and treatment often is directed towards prevention or management of complications.
- Surgical excision is advised only for functional or cosmetic reasons.
- Surgical removal may result in recurrence and multiple recurrences have been associated with malignant transformation.
- ***Complications***
 - Malignant peripheral nerve sheath tumours
 - Pheochromocytoma
 - Leukaemia
 - Rhabdomyosarcoma

Schwannoma/antoni A and antoni B bodies

(Synonyms: Neurilemmoma; neurinoma; perineural fibroblastoma)

- It is a benign neural neoplasm of Schwann cell origin.
- Bilateral neurilemmoma of auditory vestibular nerve is a characteristic feature of hereditary condition, neurofibromatosis type 2 (NF2).

Clinical features

- **Age.** Any age group.
- **Gender.** No sex predilection.
- **Location.** Head and neck region, flexor surfaces of upper and lower

extremities.

- **Signs and symptoms**
 - Slow-growing encapsulated tumour usually arises in nerve trunk.
 - As it grows, it pushes the nerve side wards.
 - Asymptomatic, but sometimes tenderness or pain may occur.
 - When it involves small nerves, it is freely movable except for a single point of attachment.
 - In large nerves, the tumour is movable except along the long axis of the nerve where the attachment restricts mobility.
 - *Oral manifestations*
 - It commonly occurs in tongue but can occur anywhere in oral cavity.
 - Soft solitary lesion, circumscribed nodular varying in size with no pathognomonic features.
 - Occasionally, tumour arises centrally within the bone and produces bony expansion of cortical plates and considerable destruction.
 - Unilocular or multilocular radiolucencies are seen.
 - Pain and paraesthesia is common.

Histopathology (fig. 2.6)

- Most of the uninodular masses are surrounded by fibrous capsules consisting of epineurium and residual nerve fibres.
- The hallmark of a schwannoma is the pattern of alternating Antoni A and Antoni B areas. The relative amounts of these two components vary and they may blend imperceptibly or change abruptly.
- Antoni A areas are composed of compact spindle cells that usually have twisted nuclei, indistinct cytoplasmic borders and occasionally clear intranuclear vacuoles. These are arranged in short bundles or interlacing fascicles. In highly differentiated Antoni A areas, there may be nuclear palisading whirling of cells and Verocay bodies, formed by two compact rows of well-aligned nuclei separated by fibrillary cell processes.
- Antoni B areas are far less orderly and less cellular. The spindle or oval cells are arranged haphazardly in the loosely textured matrix, which is punctuated by microcytic change, inflammatory cells and delicate collagen fibres. The large irregularly spaced vessels which are characteristic of schwannomas become most conspicuous in the hypocellular Antoni B areas. Their gaping tortuous lumens are often filled with thrombus material in various stages of organization and their walls are thickened by dense fibrosis.

- Occasionally, schwannomas develop cystic spaces lined Schwann cells that assume a round or epithelioid appearance, such tumours have been referred to as *pseudoglandular schwannomas.*

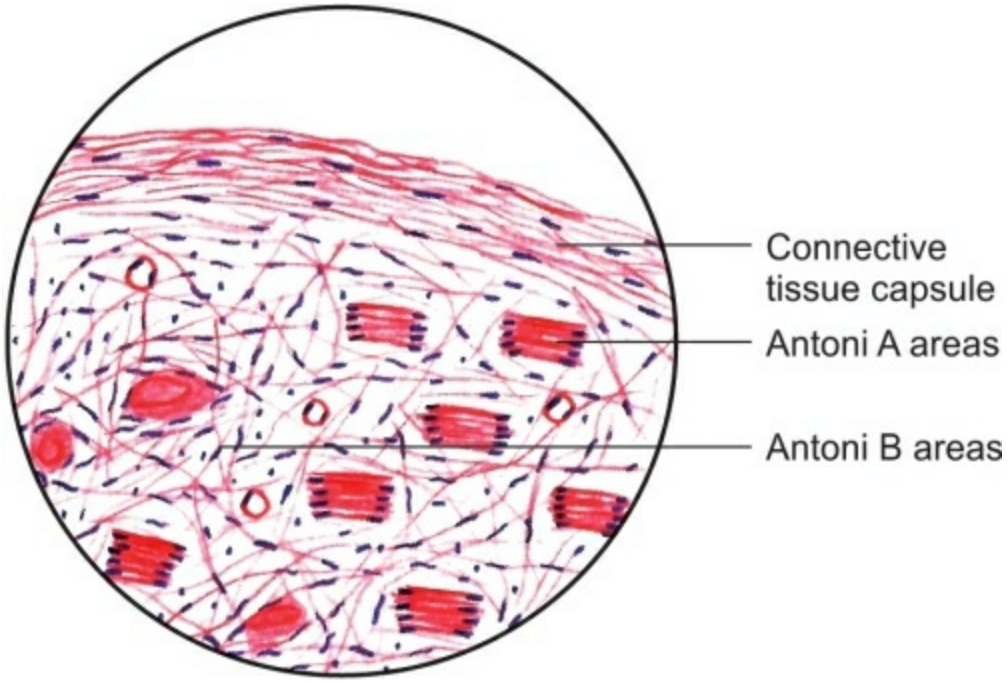


FIG. 2.6 Schwannoma.

Note: Ancient schwannoma: Degenerative changes can be seen in older tumours. These changes consist of haemorrhage, haemosiderin deposits, inflammation, fibrosis and nuclear atypia.

Prognosis and predictive factors

- Surgical excision.
- Recurrence is uncommon.

Malignant tumours of connective tissue origin

Fibrosarcoma

- Fibrosarcoma is a malignant tumour of fibroblasts.
- It is the most common soft tissue sarcoma.

Pathogenesis

- Exact aetiology is unknown.
- Inherited syndromes like multiple neurofibromas.
- Fibrous dysplasia.
- Chronic osteomyelitis.
- Bone infarcts.
- Genetic mutation: Translocation t(12; 15) (p13; q25) giving rise to ETV6–NTRK3 (ETS variant gene 6; neurotrophic tyrosine kinase receptor type 3) gene fusion.

Clinical features

- **Age.** 35–55 years.
- **Gender.** Male predilection.
- **Location**
 - Fibrosarcoma of bone: Femur, tibia.
 - Fibrosarcoma of soft tissue: Soft tissues of thigh and knee.
- **Signs and symptoms**
 - When it occurs in bone, the lesion may theoretically arise from periosteum, endosteum or periodontal ligament.
 - Slow-growing neoplasm that reaches considerable size before it produces pain.
 - Secondary ulceration may be seen as the lesion enlarges.
 - This is an infiltrative neoplasm that is more of a locally destructive problem than a metastatic problem.

Histopathology (fig. 2.7)

- Microscopically, fibrosarcoma exhibits pleomorphic spindle-shaped cells (malignant fibroblasts) typically in a herringbone or interlacing fascicular

pattern.

- Collagen may be sparse and abnormal mitotic figures are commonly seen.
- The degree of cell differentiation from one tumour to another may be quite variable.
- The periphery of this lesion is ill-defined because the neoplasm freely invades surrounding tissue.
- Fibrosarcoma is essentially a diagnosis of exclusion, and by definition there should be no expression of actin, S-100, epithelial membrane antigen, keratin or desmin.

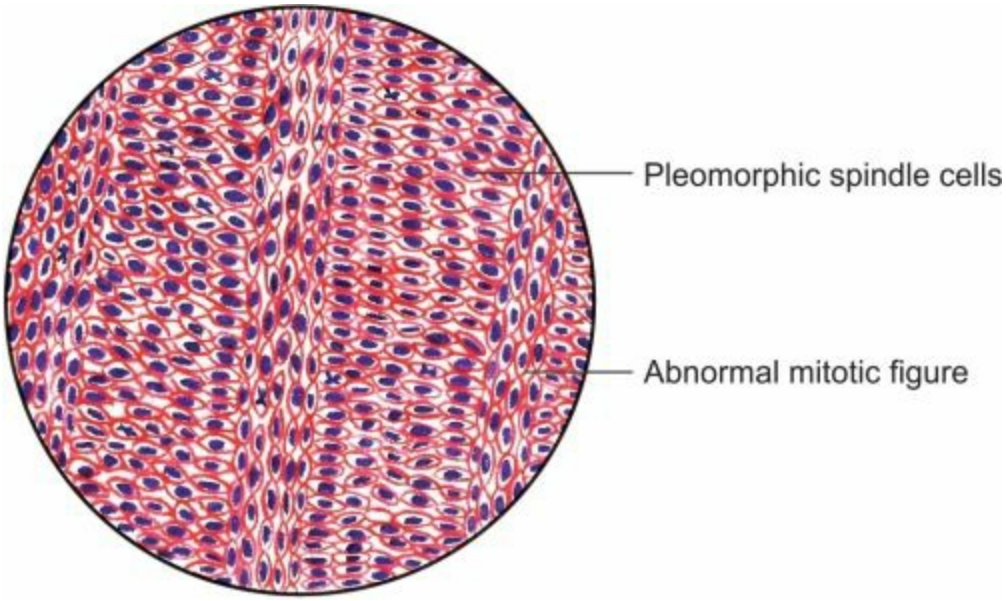


FIG. 2.7 Fibrosarcoma.

Prognosis and predictive factors

- The wide surgical excision is generally advocated for fibrosarcoma because of the difficulty in controlling local growth.
- Recurrence is common, and metastasis is infrequent.

Malignant fibrous histiocytoma

Malignant fibrous histiocytoma (MFH) is a soft tissue malignancy of late adult life.

Pathogenesis

- O'Brien and Stout postulated that cells are derived from histiocytes that could assume the appearance and function of fibroblasts (facultative fibroblasts).
- Irradiation of breast carcinoma, retinoblastoma, Hodgkin's disease and multiple myeloma.
- Postirradiation of pleomorphic sarcoma can be transformed.
- Patients exposed to phenoxy acids.
- Lynch II syndrome.

Clinical features

- **Age.** 50–70 years.
- **Gender.** Male predilection.
- **Location**
 - MFH is rarely seen in the head and neck.
 - Primarily soft tissues of extremities and retroperitoneum are involved.
- **Signs and symptoms**
 - Moderately firm submucosal mass expanding slowly with or without pain and surface ulceration.
 - Irregular nodular lesion is unencapsulated and attaches to surrounding tissues and adjacent structures.
 - Myxoid variant: Soft in consistency.
 - Angiomatoid variant: Slow growing, uni- or multinodular or cystic mass of hypodermis or subcutis.

Radiographic features

MFH reported in jaws resulting in radiolucencies with poorly defined margins.

Histopathology

- MFH shows proliferation of pleomorphic spindle cells showing fibroblastic morphology.
- Abnormal and frequent mitotic figures, necrosis and extensive cellular atypia may be seen.
- In some lesions, a storiform pattern may dominate the microscopic picture; in others, myxoid zones, giant cells, acute inflammatory cells, xanthoma cells, or blood vessels may be prominent.
- The recognition of these different microscopic features has led to the

traditional subclassification into pleomorphic-storiform, myxoid (myxofibrosarcoma), giant cell, inflammatory, and angiomatoid types.
- The prototypic form, pleomorphic-storiform MFH type, represents a heterogeneous group of malignancies which include pleomorphic variants of skeletal muscle (rhabdomyosarcoma), smooth muscle (leiomyosarcoma) and adipose (liposarcoma). Therefore, MFH has become a diagnosis of exclusion.

Prognosis and predictive factors

- The wide surgical excision is the usual treatment.
- Radiation or chemotherapy offers limited additional benefit.

Liposarcoma

- Liposarcoma is the malignant neoplasm of fatty tissue origin.
- It is the second most common soft tissue sarcoma of adult life after MFH.
- Liposarcomas of the head and neck are rare.

Pathogenesis

- The development of a liposarcoma from a pre-existing benign lipoma is rare. Most cases arise de novo.
- Chromosomal reciprocal translocation t(12; 16) (q13; p11).

Clinical features

- **Age.** Children to very elderly individuals.
- **Gender.** Male predilection.
- **Location.** The anatomical distribution of liposarcoma appears to be partly related to the histologic type.
 - Well-differentiated liposarcoma tends to occur in deep soft tissues of both the limbs and the retroperitoneum.
 - Myxoid and/or round-cell liposarcomas and pleomorphic liposarcomas have a striking predilection for the limbs and dedifferentiated liposarcoma occurs predominantly in the retroperitoneum.
 - Although any liposarcoma subtype occasionally arises in the subcutis, involvement of the dermis appears to be exceedingly rare.
 - Oral involvement is rare—tongue, submandibular area, cheek, floor of the mouth and palate are involved.

- **Signs and symptoms.** Slow growing, painless, nonulcerated submucosal mass but some lesions grow rapidly and ulcerate.

Histopathology

- Liposarcomas most frequently arise from the deep-seated stroma rather than the submucosal or subcutaneous fat.
- Liposarcomas occur in three main biologic forms:
 1. Well-differentiated liposarcoma
 2. Myxoid and/or round cell
 3. Pleomorphic
- If these occur in combination of morphologic types; these are classified as combined or mixed-type liposarcomas.
- Well-differentiated liposarcomas resemble benign lipomas and show scattered lipoblasts with atypical hyperchromatic nuclei.
- Round cell liposarcoma is aggressive and less differentiated; round cells are seen.
- Pleomorphic liposarcomas exhibit extreme cellular pleomorphism and bizarre giant cells.

Prognosis and predictive factors

- Radical excision is the treatment of choice.
- Recurrence is common.

Kaposi's sarcoma

- It was first described by *Moritz Kaposi* in *1872* in the Mediterranean basin.
- Its clinical stage depends on immune status of the patient.
- It is commonly associated with HIV/AIDS patients.

Pathogenesis

- Wahman et al's (1991) *Co-factor model*: *"The combined effects of numerous infectious agents, host factors and environmental factors encourage Kaposi's sarcoma proliferation".*
- Kaposi's sarcoma is a proliferation of endothelial cell origin.
- Human herpesvirus 8 (HHV8) or Kaposi's sarcoma herpes virus (KSHV) has been identified in all forms of Kaposi's sarcoma lesions.

Clinical features

- Four clinical presentations of Kaposi's sarcoma have been described:
 1. Classic (chronic) variant
 2. Endemic (lymphadenopathic; African) variant
 3. Immunosuppression-associated (transplant) variant
 4. AIDS-related Kaposi's sarcoma

Classic variant

- It is associated with altered immune status, lymphoreticular and other malignancies.
- It appears as multifocal reddish brown nodules primarily on the skin of the lower extremities, but any organ may be affected.
- Some lesions regress, while new ones form on adjacent or distant skin.
- Oral lesions are rare, but when it occurs it is soft, bluish nodules on palatal mucosa or gingival.

Endemic variant

- It is an endemic to young African children.
- Localized or generalized enlargement of lymph nodes including cervical nodes.
- Visceral organs are commonly involved.
- Skin and mucous membrane are rarely involved.
- It does not related to HIV.

Immunosuppression-associated (transplant) variant

- It occurs in 1–4% of renal transplant patients.
- It occurs 1 or 2 years after transplantation.
- The progression of disease correlates directly with loss of cellular immunity.
- Site: Skin, internal organs and oral mucosa (rare).

AIDS-associated Kaposi's sarcoma

- Solitary or multiple.
- Manifests on skin and oral mucosa.
- *Skin*
 - Site: Trunk, arms, head and neck.
 - Macular, nodular or raised and ulcerated, the colour of which range

from red to purple.
 - Early lesions appear flat red and asymptomatic.
 - Colour becomes darker as lesion ages.
- *Oral mucosa*
 - Lesions begin as brown or reddish purple macular lesions that do not blanch with pressure.
 - With time, the macule develops into plaque or nodules.
 - Pain, bleeding and necrosis may occur.

Oral manifestations

- Sites: Gingiva, tongue, uvula, tonsils, pharynx and trachea.
- Flat and slightly blue, red or purple plaques are seen. It may be either focal or diffuse.
- Initially lesions are asymptomatic, which progress to more deeply discoloured, surface papules and soft nodules or exophytic and ulcerated lesion, which may bleed.
- Oral candidiasis and AIDS-related gingivitis may be seen.
- It may interfere with mastication, phonation, tooth loss and airway obstruction.

Histopathology

Patch stage: Early lesion

- It is characterized by proliferation of small veins and capillaries around one or more pre-existing blood vessels.
- Slit-like vessels are present around pre-existing blood vessels, skin adnexa and between collagen fibres.
- Vessels are lined by plump, mildly atypical endothelial cells.
- Pronounced mononuclear inflammatory cell infiltrate including mast cells, scattered RBCs and haemosiderin deposits may be present.
- Perivascular proliferation of spindle cells and cellular atypia is minimal.

Plaque stage: Advanced stage

- Increased numbers of small capillaries or dilated vessels interspersed with proliferating sheets of sarcomatous or atypical spindle cells are seen.
- Large numbers of extravasated RBCs and abundant haemosiderin deposition are seen.
- Slit-like vascular channels without a visible endothelial lining are interspersed with spindle cells.
- Lesional cells are enlarged, hyperchromatic nuclei with mild to moderate

pleomorphism with minimal mitotic activity.

Nodular stage: More advanced lesion

- All histologic features are more prominent than plaque stage.
- Spindle cells increase to form a nodular tumour-like mass that resembles fibrosarcoma.
- Numerous extravasated RBCs are present.
- Slit-like vascular spaces may be seen.

Differential diagnosis

- Haemangioma
- Erythroplakia
- Melanoma

Prognosis and predictive factors

- Surgery has been useful on localized lesions and low-dose radiation and intralesional chemotherapy can also be used.
- For larger and multifocal lesions, systemic chemotherapeutic regimens are being used.

Ewing's sarcoma

(Synonyms: Endothelial myeloma; round cell sarcoma)

- Ewing's sarcoma is a highly lethal round cell sarcoma.
- It was first described by *James Ewing* in *1921.*
- Ewing's sarcoma accounts for approximately 6% of all malignant bone tumours and represents third most common osseous neoplasm after osteosarcoma and chondrosarcoma.

Definition

Highly malignant, small round to oval cell sarcomas with the clinical and radiographic characteristics of a primary osseous lesion *(Unni, 1996).*

Pathogenesis

- The cause is unknown, the cell of origin is uncertain.
- It is related to the primitive neuroectodermal tumour (PNET), sharing a common karyotype translocation t(ll; 12) (q24; q12) in approximately 90% of these tumours.

Clinical features

- **Age.** 5–30 years.
- **Sex.** Males predilection.
- **Location**
 - Long bones, pelvis and ribs are commonly affected.
 - Jaws—ramus of the mandible.
- **Signs and symptoms**
 - Pain and swelling are the most common presenting symptoms.
 - Fever, leukocytosis and an elevated ESR may be present.
 - The tumour commonly penetrates the cortex, resulting in a soft tissue mass overlying the affected area of bone.
 - Facial neuralgia and lip paraesthesia have been reported in jaw involvement.
 - Loosening of teeth and mucosal ulcers are seen.

Radiographic findings

- Radiographic appearance is suggestive but not pathognomonic of disease.
- The lesion is a destructive one and produces an irregular, diffuse radiolucency, although lesions of jaw resemble sclerosing osteomyelitis.
- A common characteristic feature is the formation of layers of new subperiosteal bone producing the *'onion-skin' appearance.*
- Moth-eaten radiolucency of the medullary bone and erosion of the cortex with expansion is seen.

Histopathology

- It is an extremely cellular neoplasm composed of solid sheets or masses of small round cells with very little stroma, although a few connective tissue septa may be present.
- Cells are small and round in shape with scanty cytoplasm and relatively large round to oval nuclei with finely dispersed chromatin and hyperchromasia.
- The sarcoma cells are arranged in filigree pattern.
- Mitotic figures are common.
- Haemorrhage with vascular lakes or sinuses may be seen.

Differential diagnosis

- Lymphoma

- Metastatic neuroblastoma
- Osteosarcoma

Prognosis and predictive factors

- Metastasis especially to lungs, other bones and lymph nodes is common.
- Multimodality treatment protocols, involving surgery or radiation for local control and chemotherapy for systemic micrometastases have dramatically improved.

Chondrosarcoma

Chondrosarcoma is the malignant counterpart of the chondroma.

Pathogenesis

- The exact origin is unknown but basic proliferating tissue is cartilage.
- Primary chondrosarcomas arise de novo in extraskeletal tissues or in teratomas or mixed tumours.
- Secondary chondrosarcomas arises from the pre-existing tumour and dedifferentiated tumours like osteosarcomas, fibrosarcomas and malignant fibrous histiocytoma.
- Chromosomal translocations (chromosomes 13 and 21) have been reported in skeletal and extraskeletal mesenchymal chondrosarcomas.

Clinical features

- **Age.** 10–80 years.
- **Gender.** Male predilection.
- **Location**
 - Lesions arising in the maxilla involve the anterior region (lateral incisor–canine region) and the palate.
 - Mandibular chondrosarcomas occur most often in the premolar and molar regions, symphysis, coronoid process and occasionally the condylar process.
- **Signs and symptoms**
 - Slow clinical evolution.
 - The most common signs are painless swelling and expansion of the affected bones, resulting in loosening of teeth or ill-fitting dentures.
 - Pain, visual disturbances, nasal signs and headache may result from

extension of chondrosarcomas from the jaw bones to contiguous structures.
- Metastases are rare.

Radiographic features

- The radiographic appearance of chondrosarcoma varies from moth-eaten radiolucencies that are solitary or multilocular to diffusely opaque lesions.
- Many chondrosarcomas contain mottled densities corresponding to areas of calcification and ossification.

Histopathology

- Chondrosarcoma composed of cartilage showing varying degrees of maturation and cellularity.
- Usually typical lacunar formation within the chondroid matrix is seen, although this feature may be scare in poorly differentiated tumours.
- The tumour often shows a lobular growth pattern with tumour lobules separated by thin fibrous connective tissue septa.
- The central areas of the lobules demonstrate the greatest degree of maturation.
- The peripheral areas consist of immature cartilage and mesenchymal tissue consisting of round or spindle-shaped cells.
- Calcification or ossification may occur within the chondroid matrix.

Grading

Pathologic grading of chondrosarcomas is as follows:

- *Grade I* tumours show hypocellular with moderate cytologic atypia.
- *Grade II* tumours often have a myxoid stroma with enlarged chondrocyte nuclei displaying occasional mitotic figures. Increased cellularity is often noted at the periphery of the cartilaginous lobules.
- *Grade III* tumours are markedly cellular; often with a spindle cell component. Mitotic figures may be numerous.

Differential diagnosis

- Osteosarcoma
- Pleomorphic adenoma
- Chondromyxoid fibroma

Prognosis and predictive factors

- Chondrosarcomas are radioresistant neoplasms, so wide local or radical surgical excision is the treatment of choice.
- The location of the primary lesion and the adequacy of surgical resection (tumour-free margins) are of prime prognostic significance for chondrosarcomas of the jaws.
- The most common cause of death due to chondrosarcomas of the jaws is uncontrolled local recurrence and extension into adjacent vital structures.

Osteosarcoma

(Synonym: Osteogenic sarcoma)

Osteosarcomas account for approximately 20% of all sarcomas and are a malignancy of mesenchymal cells. These are the most common primary bone tumours.

Pathogenesis

- The molecular mechanism associated with osteosarcoma pathogenesis appears to be related to mutations or amplifications of one or more genes.
- Alterations in *p53, Rb* (retinoblastoma), *CDK4* (cyclin-dependent kinase 4), *MDM2* (murine double minute 2), c-*fos, cmyc,* and *SAS* (sarcoma amplified sequence) genes have all been cited as contributing to osteosarcoma development.
- Protein expression of the defective/amplified genes results in loss of control of cell proliferation and differentiation.
- Osteosarcomas arise in pre-existing bone abnormalities such as *Paget's disease, fibrous dysplasia, giant cell tumour, multiple osteochondromas, bone infarct, chronic osteomyelitis* and *osteogenesis imperfecta*. Some osteosarcomas have also been preceded by radiation therapy to the affected bone for unrelated or antecedent disease.

Clinical features

- **Age.** Osteosarcoma demonstrates a bimodal age distribution. It arises in individuals between the age of 10 to 20 years and above 50 years.
- **Gender.** Male predilection.
- **Location.** The mandible is more commonly affected than the maxilla. Mandibular tumour involves symphysis, angle of mandible and ascending

ramus. Maxillary tumour involves alveolar ridge, maxillary antrum, palate, zygoma and orbital rim.

- **Signs and symptoms**
 - Swelling and pain, particularly with activity of the involved bone, are the early features of the neoplasm.
 - Patients may complain of a sprain, arthritis or growing pain.
 - Systemic symptoms such as fever and night sweats are rare.
 - Pathological fractures are common.
 - Osteosarcomas involving the jaws present most commonly with swelling and localized pain. In some cases, there may be loosening and displacement of teeth, as well as paraesthesia due to involvement of the inferior alveolar nerve.
 - Maxillary tumours cause paraesthesia of the infraorbital nerve, epistaxis, nasal obstruction, proptosis and diplopia.

Radiographic features

- Early osteosarcomas that involve the alveolar process may be characterized by localized widening of the periodontal ligament space of one or two teeth. The widened space results from tumour invasion of the periodontal ligament and resorption of the surrounding alveolar bone.
- Advanced tumours can be visualized as *moth-eaten* radiolucencies or irregular, poorly marginated radiopacities. The majority of these neoplasms have mixed radiographic features. A characteristic *sun ray* or *sunburst* radiopaque appearance due to periosteal reaction may be seen in jaw lesions but is not diagnostic of osteosarcoma.

Histopathology (fig. 2.8)

- Osteosarcomas shows sarcomatous stroma and tumour osteoid formation.
- Tumour cells vary from uniform round or spindle cells to highly pleomorphic cells with bizarre nuclear and cytoplasmic shapes.
- Variable histologic patterns are seen based on their production of osteoid, chondroid and fibres as *osteoblastic, chondroblastic* and *fibroblastic,* respectively. An additional variant, designated as *telangiectatic,* that displays multiple aneurysmal blood-filled spaces lined by malignant cells.
- Chondroblastic variant consists of cartilage growing in globule with small foci of direct osteoid production by tumour cells.
- *Low-grade well-differentiated osteosarcoma* is characterized by minimal cellular atypia of lesional cells and abundant bone formation.

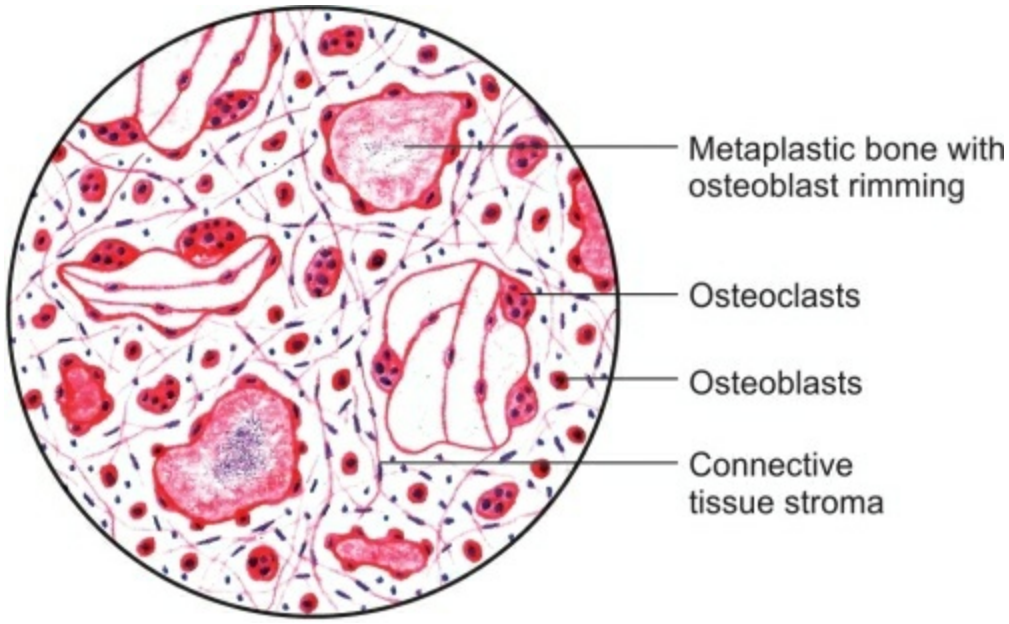


FIG. 2.8 Osteosarcoma.

Differential diagnosis

- Chondrosarcoma
- Fibrosarcoma
- Malignant fibrous histiocytoma of bone

Prognosis and predictive factors

- The management of sarcomas of the facial skeleton involves both surgery and chemotherapy.
- Surgical management of osteosarcoma is the mainstay of therapy.
- Chemotherapy may be administered preoperatively (neoadjuvant chemotherapy) or postoperatively (adjuvant chemotherapy).
- Conservative management of sarcomas will lead to local recurrence and increase the tendency for distant metastasis.

Multiple myeloma and other plasma cell neoplasms

- Plasma cell neoplasms are derived from bone marrow stem cells of B lymphocyte lineage and these are functionally differentiated in their ability to produce immunoglobulin.
- Tumours may present in soft tissue as *extramedullary plasmacytoma*, in bone as a solitary lytic lesion known as *plasmacytoma of bone* or commonly, as part of the multifocal disseminated disease *multiple myeloma*.

Pathogenesis

- It is a prototype of monoclonal malignancies of plasma cells.
- Mutation of terminally differentiated B cells or early committed B cells leads to more differentiated plasma cells.
- *Predisposing factors:* Radiation exposure, occupational exposure in agriculture, chemical, rubber plant and paper workers and chemical exposure of benzene, formaldehyde, hair dyes, plant sprays and asbestos.
- Specific translocation includes t(11;14), t(14;18) and t(8;14) with abnormal expression of bcl-2 protein.
- Mutations of the *ras* oncogene and *p53* gene have been reported.

Clinical features

- **Age.** 50–65 years.
- **Gender.** Male predilection.
- **Location**
 - 80% of extramedullary plasmacytomas involve the head and neck region with a predilection for the nasopharynx, nasal cavity, paranasal sinuses and tonsils.
 - The tumours have also been reported in the gingiva, palate, floor of the mouth and tongue.
 - Solitary plasmacytoma of bone is rare in the jaws; it more commonly appears in the ileum, femur, humerus, thoracic vertebrae and skull.
- **Signs and symptoms**
 - Involvement of the jaws may be asymptomatic or may produce pain, swelling, expansion, numbness, mobility of teeth, or pathologic fracture or an associated soft tissue mass.
 - Some patients may exhibit weakness, weight loss, anaemia and hyperviscosity syndromes.
 - 10% of patients with multiple myeloma develop *systemic amyloidosis.*
 - Pathologic fractures occur in 20%of patients.
 - Advanced disease is associated with hypercalcaemia and renal failure.

Radiographic features

Multiple well-defined, punched-out radiolucencies or ragged radiolucent lesions may be seen. These may be especially evident on a skull radiograph.

Lab investigations

- The production of monoclonal immunoglobulin components by the neoplastic plasma cells results in an excess of abnormal protein that circulates in serum and can often be detected in urine.
- On serum protein electrophoresis, most patients with myeloma are found to have a decreased quantity of normal immunoglobulin and an abnormal monoclonal immunoglobulin protein peak, known as an *M spike.* The immunoglobulin is usually of the IgG or IgA class, with a monoclonal light-chain component.
- Urinary monoclonal light chains, called Bence Jones proteinuria, may be detected in approximately 50% of patients with myeloma.

Histopathology

- Tumours are composed of a monotonous proliferation of neoplastic plasma cells that show a wide range of differentiation, from mature-appearing plasma cells to less well-differentiated forms resembling immunoblastic large cell lymphomas.
- Typically plasma cells are round or ovoid cells with eccentrically placed nuclei exhibiting chromatin clumping in a cast wheel or checkerboard pattern.
- Mitotic activity may be seen with some frequency.
- Russell bodies are commonly seen.

Differential diagnosis

- Lymphoma
- Leukaemia
- Metastatic malignant melanoma

Prognosis and predictive factors

Multiple myeloma is treated with chemotherapeutic alkylating agents and steroids, with local radiation directed to painful bone lesions.

Non-hodgkin's lymphoma

The non-Hodgkin's lymphomas (NHL) are a heterogenous group of lymphoproliferation malignancies which can involve both lymph nodes and lymphoid organs as well as extranodal organs and tissues.

Classification

Rappaport classification

- *Low grade*
 - Diffuse lymphocytic, well-differentiated (DLWD)
 - Nodular lymphocytic, poorly differentiated (NLPD)
 - Nodular mixed, lymphocytic and histiocytic (NM)
- *Intermediate grade*
 - Nodular histiocytic (NH)
 - Diffuse lymphocytic, poorly differentiated (DLDP)
 - Diffuse mixed, lymphocytic and histiocytic (DM)
 - Diffuse histiocytic (DH)
- *High grade*
 - Diffuse histiocytic (DH)
 - Diffuse lymphoblastic (DL)
 - Diffuse undifferentiated Burkitt's or non-Burkitt's (DU)

Pathogenesis

- **Genetic abnormalities:** The t(11; 14) (q13; q32) translocation results in overexpression of bcl-1 (cyclin D1/PRAD1), a cell cycle control gene on chromosome band 11q13.
- **Environmental factors**
 - Chemicals:
 - Pesticides and herbicides, e.g. organophosphates, chlorophenols
 - Solvents and organic chemicals, e.g. benzene, carbon tetrachloride
 - Patients who receive cancer chemotherapy and/or radiation therapy.
- **Viruses**
 - Epstein–Barr viruses in Burkitt's lymphoma, sinonasal lymphoma and lymphomas in immunocompromised patients.
 - HTLV-1 in adult T cell lymphoma or leukaemia.
 - HHV-8 in body cavity–based lymphomas in patients with HIV infection.
- **Immunodeficiency states**
 - Congenital immunodeficiency states: Ataxia, telangiectasia, Wiskott–Aldrich syndrome and hypoglobulinemia.
 - Acquired immunodeficiency states: HIV infection, solid organ or bone marrow transplant recipients.
- **Connective tissue disorders:** Sjögren's syndrome, rheumatoid arthritis and systemic lupus erythematosus.

Clinical features

- **Age.** >50 years.
- **Gender.** Male predilection.
- **Signs and symptoms**
 - Lymphadenopathy: Non-tender mass that slowly enlarging for months.
 - Cervical, axillary, inguinal lymph nodes are involved.
 - Initially, one or two freely movable nodules are seen.
 - As malignancy progresses, the nodes become more numerous and are fixed to adjacent structures or matted together.
 - Gradually, the process involves other lymph node groups and invasion of adjoining normal tissues occurs.
 - Systemic symptoms: Fever, night sweats, weight loss, fatigue and pruritis.
 - Organ specific symptoms: Shortness of breath, chest pain, cough, abdominal pain and bone pain are seen.
 - Neurological symptoms are important because CNS involvement may occur in aggressive lymphomas.
 - *Oral manifestations*
 - Soft tissue involvement: It is characterized by swellings which may grow rapidly and then ulcerate. It commonly affects the buccal vestibule, posterior hard palate or gingiva. In some cases, these become large, fungating, necrotic, foul smelling masses.
 - Bone involvement: When underlying bone is involved, tooth mobility, pain and paraesthesia may develop.

Radiographic features

- *Initial stages:* Ill-defined or ragged radiolucency.
- *Later stages:* Expansion of bone eventually perforating the cortical plate and producing a soft tissue swelling.

Staging

Ann Arbor system for classification of non-Hodgkin's lymphoma

- *Stage I:* The lymphoma is only in one group of lymph nodes in one particular area of the body.
- *Stage II:* More than one group of lymph nodes is affected, but all the affected nodes are contained within either the upper half or lower half of the body:

 - The upper half of the body: Above the diaphragm.
 - The lower half of the body: Below the diaphragm.
- *Stage III:* Lymphoma is present in lymph nodes in both the upper and lower parts of the body. Spleen is considered as a lymph node in this staging system.
- *Stage IV:* The lymphoma has spread beyond lymph nodes to other organs, i.e. to sites such as the nervous system, bone marrow, liver or lungs.

Histopathology

- It is characterized by a proliferation of lymphocytic appearing cells that may show varying degrees of differentiation, depending on the type of lymphoma.
- *Low-grade lesions* consist of well-differentiated small lymphocytes. *High-grade lesions* are composed of less-differentiated cells.
- It may be nodular or diffuse pattern:
 - *Nodular or follicular pattern:* The neoplastic cells tend to aggregate in such a way that large clusters of cells are seen.
 - *Diffuse pattern:* Monotonous distribution of cells with no evidence of nodularity or germinal centre formation. It produces an entire effacement of normal lymph node architecture.

Differential diagnosis

- Burkitt's lymphoma
- Metastatic neuroblastoma
- Acute leukaemia

Prognosis and predictive factors

- NHL can be treated with radiotherapy, chemotherapy or biologic therapy.
- NHL can be divided into two prognostic groups:
 1. *Indolent lymphomas:* Good prognosis, but they usually are not curable in advanced clinical stages.
 2. *Aggressive lymphomas:* Poor prognosis, but a significant number of these patients can be cured with intensive combination chemotherapy regimens.

Burkitt's lymphoma

(Synonym: African jaw lymphoma)

- Burkitt's lymphoma is a high-grade non-Hodgkin's lymphoma, which is endemic in Africa.
- It was first recognized in 1958 by *Dennis Burkitt* in Uganda as a jaw malignancy occurring with high frequency in African children.
- The endemic and sporadic forms of Burkitt's lymphoma are histologically and immunophenotypically identical.

Pathogenesis

- Both sporadic and endemic forms of Burkitt's lymphoma are characterized by a translocation of the distal part of chromosomes 8 to 14.
- The former is the site of the *c-myc* oncogene, and the latter, the immunoglobulin heavy-chain locus.
- This translocation may be directly involved in the enhanced tumour cell proliferation of Burkitt's lymphoma, which has been shown to have the highest proliferation rate of any neoplasm in humans.

Clinical features

- Endemic form of Burkitt's lymphoma present with swelling of affected jaw or other facial bones, loosening of teeth, paraesthesia, swelling of lymph nodes which are not tender and rapidly growing in the neck or below the jaw. Abdominal presentation uncommon.
 Site: Maxilla: mandible ratio of 2:1.
- Sporadic form of Burkitt's lymphoma: Abdominal tumours are commonly present causing swelling and pain in the affected area. Some patients present with symptoms of bowel obstruction secondary to an ileocecal intussusception caused by tumour growth.
 Site: Distal ileum, cecum and pelvic organs.
- Rapid growth may lead to metabolic derangement and renal function impairment.
- Rare cases present as acute leukaemia with fever, anaemia, bleeding and adenopathy.
- The tendency of jaw involvement seems to be age related; 90% of 3-year-old patients have jaw lesions, in contrast to only 25% of patients older than age 15.

Radiographic features

- Moth-eaten, poorly marginated destruction of bone is observed.
- The cortex may be expanded, eroded or perforated with soft tissue involvement.

Histopathology

- Burkitt's lymphoma is a monoclonal proliferation of B lymphocytes characterized by small noncleaved cells that are uniform in appearance and that produce a diffuse pattern of tissue involvement.
- Burkitt's cells are homogenous in size and shape, with round to oval nuclei and slightly coarse chromatin with multiple nucleoli and with intensely basophilic vacuolated cytoplasm that contains neutral fat.
- Mitotic figures are frequently seen.
- On viewing the lesion on low power magnification, a classic starry sky pattern is appreciated. It is a phenomenon that is caused by the presence of macrophages within the tumour tissue. These macrophages have abundant cytoplasm, which microscopically appear less intensely stained in comparison with the surrounding process. Thus, these cells tends to stand out as 'stars' set against the 'night sky' of deeply hyperchromatic neoplastic lymphoid cells.

Differential diagnosis

- Non-Hodgkin's lymphoma
- Metastatic neuroblastoma
- Acute leukaemia

Prognosis and predictive factors

- Burkitt's lymphoma was at one time invariably fatal within 4–6 months of diagnosis.
- However, because of its high proliferation rate, Burkitt's lymphoma has proved to be extremely sensitive to combination chemotherapy and is therefore potentially curable.
- The endemic and sporadic forms of Burkitt's lymphoma show similar complete response rates to chemotherapy, with similar rates of relapse and survival.

Hodgkin's lymphoma

(Synonyms: Hodgkin's disease; malignant lymphoma)
It was first described by Thomas Hodgkin in 1832.

Pathogenesis

- Unknown.
- Infectious agents: Epstein–Barr virus.
- Genetic predisposition: 1% of Hodgkin's disease (HD) patients.

Clinical features

- **Age.** Bimodal age incidence: Young adults—15 to 35 years
 Older adults—45 to 75 years
- **Gender.** Male predilection.
- **Signs and symptoms**
 - It starts in one lymph node group, unifocal origin, and spreads in a predictive manner to the adjacent lymph node group—contiguous spread.
 - Lymph nodes are discrete, non-tender and rubbery consistency. Alcohol-induced discomfort is a diagnostic feature.
 - Compression of various organs by lymph node masses causes dysphagia, dyspnoea, Horner's syndrome, hoarseness of voice, superior vena caval syndrome, inferior vena caval obstruction, jaundice and paraplegia.
 - B symptoms or systemic symptoms
 - Unexplained weight loss
 - Unexplained fever
 - Heavy night sweats
 - Hepatosplenomegaly.
 - Pel–Ebstein fever/cyclical pattern fever—several days or weeks of fever alternating with afebrile periods.
 - It may result in high-risk infections like herpes zoster, tuberculosis, cytomegalovirus infection and candidiasis.
 - Oral manifestations: Rare, because it is primarily a disease of lymph node.

Staging

Ann Arbor system for classification of Hodgkin's lymphoma

- *Stage I:* Involvement of single lymph node region (I) or a single

extralymphatic organ or site (IE).

- *Stage II:* Involvement of two or more lymph node regions on the same side of diaphragm (II).

or

One or more lymph node regions with an extralymphatic site (IIE).

- *Stage III:* Involvement of lymph node regions on both sides of the diaphragm (III), possibly with an extralymphatic organ or site (IIIE), the spleen (IIIS) or both (IIISE)
- *Stage IV:* Diffuse or disseminated involvement of one or more extralymphatic organ with or without associated lymph node involvement.
- Stages I, II, II, IV can be subclassified into A and B categories:
 - A: Absence of systemic signs.
 - B: Presence of fever, night sweats and/or unexplained loss of 10% or more body weight during the 6 months period (B symptoms).

Histopathology

- Loss of normal nodal architecture by a diffuse, often mixed infiltrate of inflammatory cells that is interspersed with large, atypical neoplastic lymphoid cells—*Reed–Sternberg cells.*
- **Reed–Sternberg (RS) cells**
 - These are characteristic large malignant cells in Hodgkin's lymphoma.
 - 20–50 μm in diameter, abundant, amphophilic, finely granular or homogenous cytoplasm.
 - Two mirror image nuclei (owl eyes) each with an eosinophilic nucleolus and a thick nuclear membrane (chromatin is distributed at the cell periphery) or may be multinucleated.
 - $CD15^+$ and $CD30^+$ immunophenotypes.
 - These atypical cells are not diagnostic of Hodgkin's lymphoma because similar cells may be seen in viral infections especially infectious mononucleosis.
- Histopathologic types of Hodgkin's lymphoma, based on RS cells:
 - Nodular lymphocyte predominant Hodgkin's lymphoma
 - Classical Hodgkin's lymphoma
 - Lymphocyte rich
 - Nodular sclerosis
 - Mixed cellularity
 - Lymphocyte depletion

- Unclassifiable
- Nodular lymphocyte predominant Hodgkin's disease:
 - It consists of small lymphocytes, epithelioid histiocytes and lymphocytic and histiocytic (L and H) cells.
 - RS cells: The lymphocytic and histiocytic cells (L and H) or popcorn cells (their nuclei resemble an exploded kernel of corn) are seen within a background of inflammatory cells predominantly of lymphocytes.
 - L and H cells are large cells with very little cytoplasm. The enlarged nuclei have vesicular chromatin and may have irregular nuclear contours which led to describe as *popcorn* or *elephant ear* cells. It contains one to multiple nucleoli that are smaller and less eosinophilic.
- Lymphocyte-rich classic Hodgkin's disease
 - RS cells: Classic or lacunar type with a background of lymphocytic infiltrate.
 - Some cases show nodular pattern.
- Nodular sclerosis Hodgkin's disease
 - It shows nodular pattern. The broad bands of fibrosis divide the node into nodules.
 - The capsule will be thickened.
 - RS cells: Lacunar type, monolobated or multilobated nucleus and a small nucleolus with abundant and pale cytoplasm.
- Mixed cellularity Hodgkin's disease
 - RS cells: Classic type, a large with bilobate, double or multinuclei and large eosinophilic nucleolus.
 - Diffuse infiltration of inflammatory cells is seen.
- Lymphocyte depleted Hodgkin's disease
 - Large numbers of RS cells and bizarre sarcomatous variants are present.
 - Hypocellular and diffuse infiltration of inflammatory cells are seen.
 - It is an advanced stage disease.
 - Epstein–Barr virus proteins are expressed.
- Unclassifiable Hodgkin's disease
 - Occasionally, HD do not fit the criteria for any of the known subtypes and these are designated as unclassifiable variant.

Prognosis and predictive factors

- Radiotherapy: Stage I and stage II.
- Chemotherapy: MOPP—mechlorethamine, oncovin, procarbazine and prednisone.

- Combination of radiotherapy and chemotherapy: Stage III and stage IV.
- Prognosis
 - Lymphocyte predominant—good prognosis
 - Nodular sclerosis—favourable prognosis
 - Mixed cellularity—poor prognosis
 - Lymphocyte depletion—least favourable prognosis

Leiomyosarcoma

- Leiomyosarcoma is a malignant neoplasm of smooth muscle origin.
- It accounts for 7% of all soft tissue sarcomas.
- Leiomyosarcoma of the oral cavity is rare.

Pathogenesis

- It develops through malignant transformation of leiomyoma or de novo.
- It arises from smooth muscle cells those found in blood vessel walls and from undifferentiated mesenchymal cells.
- *Wang et al* suggested 13q14–q21 loss and 5p14 gain.

Clinical features

- **Age.** Middle age and older adults.
- **Gender.** No sex predilection.
- **Location.** Jaw bones, cheek and floor of the mouth.
- **Signs and symptoms**
 - Painful lobulated fixed mass of submucosal tissue.
 - Usually less than 2 cm in diameter.
 - Slow growing but secondary ulceration of surface is also seen.

Histopathology

- Fascicles of spindle-shaped cells with abundant eosinophilic cytoplasm and blunt-ended cigar-shaped nuclei.
- Epithelioid leiomyosarcoma: Consists of rounded epithelioid cells with eosinophilic or clear cytoplasm.
- Mitoses: Five or more in ten high power fields.
- Glycogen is demonstrated with PAS stain, cytoplasm appears bright red with Masson-trichrome stain; longitudinal striations are seen with PTAH.
- Immunohistochemistry demonstrates desmin, muscle-specific actin and

smooth muscle actin positivity.

Prognosis and predictive factors

- Radical surgical excision with adjunctive chemotherapy and radiotherapy.
- Prognosis is poor with high recurrence rate and distant metastasis.

Rhabdomyosarcoma

Rhabdomyosarcoma is malignant neoplasm of skeletal muscle origin.

Types

There are four types of rhabdomyosarcoma based on histopathologic appearance:
1. Pleomorphic
2. Alveolar
3. Embryonal: Commonly occurs in head and neck region
4. Botryoid

Pathogenesis

- It develops through malignant transformation of rhabdomyoma or de novo.
- According to *Rubin,* it is derived from primitive mesenchyme that retains the capacity for skeletal muscle differentiation.
- Embryonal rhabdomyosarcoma: Loss of heterozygosity of chromosome 11p15.
- Alveolar rhabdomyosarcoma: Translocation occurs between *FKHR* gene on chromosome 13 and *PAX3* gene on chromosome 2 or *PAX7* gene on chromosome 1.

Clinical features

Embryonal rhabdomyosarcoma
It constitutes 60–70% of all rhabdomyosarcomas.

- **Age.** 16 days to 14 years.
- **Gender.** No sex predilection.
- **Location**
 - Genitourinary region.
 - Head and neck region: Tongue, orbit, inner canthus, cheek, tonsil, soft

palate, mastoid, mucobuccal folds, internal ear, temporal and cervical regions and floor of the mouth.

Botryoid rhabdomyosarcoma

It constitutes 10% of all rhabdomyosarcomas.

- **Age.** Young children.
- **Gender.** No sex predilection.
- **Location.** Vagina, prostate, maxillary sinus, nasopharynx and middle ear.

Alveolar rhabdomyosarcoma

It constitutes 20% of all rhabdomyosarcomas.

- **Age.** 5 months to 50 years.
- **Gender.** No sex predilection.
- **Location.** Extremities, and head and neck region.

Pleomorphic rhabdomyosarcoma

It is a least common variant.

- **Age.** Older individuals, average age of 50 years.
- **Gender.** Male predilection.
- **Location.** Extremities, and head and neck region.
- **Signs and symptoms**
 - Rapidly enlarging swelling and pain is present, if nerve is involved.
 - Depending upon site of lesion, divergence of an eye, abnormal phonation, dysphagia, cough, aural discharge or deviation of jaw are seen.
 - Occasionally ulcerate and may invade underlying bone and develop distant metastasis.
 - Exophytic polypoid growth can be seen in botryoid (grape-like) variant.

Histopathologic features

Embryonal rhabdomyosarcoma

- Eosinophilic spindle cells are arranged in interlacing fascicles.
- Round eosinophilic cells, large and intermediate in size with a small nucleus and a granular eosinophilic cytoplasm.
- Broad elongated eosinophilic cells with cross-striations.
- Small round and spindle cells with dark staining nuclei and little cytoplasm.
- More well-differentiated tumours show strap or tadpole-shaped rhabdomyoblasts.

Botryoid rhabdomyosarcoma

- Diffuse myxoid or mucoid matrix with sparsely scattered primitive

mesenchymal cells.
- Peripheral zone of increased cellularity called as *cambium layer* is seen.

Alveolar rhabdomyosarcoma
- Small, poorly differentiated round and oval cells are aggregated into irregular clusters or nests separated by fibrous septa.
- Degenerated cells in the centre show lack of cohesiveness, while the peripheral cells are arranged in a single layer against the septal walls.
- Multinucleated giant cells and mitotic figures are common.

Pleomorphic rhabdomyosarcoma
- Loosely arranged haphazardly oriented cells of variable morphology.
- Deeply eosinophilic cytoplasm with small and large round cells with pleomorphic shapes is seen.

Prognosis and predictive factors
- Radical surgical excision
- Multiagent chemotherapy
- Postoperative radiotherapy

Malignant peripheral nerve sheath tumour

(Synonyms: Malignant schwannoma; malignant neurilemmoma; neurogenic sarcoma; neurofibrosarcoma)

Spindle cell malignancy of peripheral nerve Schwann cells.

Pathogenesis
- Malignant peripheral nerve sheath tumour (MPNST) may develop in patients with neurofibromatosis 1.
- It may be associated with irradiation.

Clinical features
- **Age.** 20–50 years.
- **Gender.** Male predilection.
- **Location**
 - Head and neck region.
 - Oral cavity: Tongue, soft palate, lip, gingiva and buccal mucosa.
 - Central tumours: Mandibular nerve is more commonly involved.
- **Signs and symptoms**

- Asymptomatic except presence of mass. Sometimes, pain and/or paraesthesia, muscle weakness may be present.
- At surgery, usually mass attached to main trunk and surgeon may note cystic degeneration or haemorrhage within lesional stroma.

Radiographic features

- Diffuse radiolucency, which is a characteristic feature of malignant infiltration.
- If mandibular nerve is involved, dilatation of mandibular canal is seen.

Histopathology

- It is composed of spindle cells demonstrating a wavy or comma-shaped outline and nuclear contour of Schwann cells.
- Cellular and nuclear pleomorphism will be prominent.
- High mitotic activity is seen.
- Spindle cells are arranged in sweeping fascicles interspersed with hypocellular and myxoid regions.
- It is categorized into three patterns: (i) *epithelioid, (ii) mesenchymal and (iii) glandular.*
- *Epithelioid variant* shows plump, rounded or ovoid epithelioid cells scattered throughout the lesional spindle cells having a vesicular or hyperchromatic nuclei.
- *Mesenchymal variant* shows a plump, rounded or strap cells with eosinophilic, fibrillar and with cross-striated cytoplasm resembling a rhabdomyoblastic differentiation. It is commonly termed as *triton tumour.*
- *Glandular variant* shows well-differentiated ductal structures lined by simple, stratified, cuboidal or columnar epithelial cells with occasional goblet cells.

Differential diagnosis

- Leiomyosarcoma
- Fibrosarcoma
- Monophasic synovial sarcoma

Prognosis and predictive factors

- Wide surgical excision is done.
- Local recurrences are common and haematogenous metastases are seen.

- Tumour is resistant to chemotherapy and radiotherapy.
- Overall survival rate is 40–75%.

Key points

- *Squamous papilloma* results from infection of human papilloma virus.
- *Koilocytes* are HPV-altered epithelial cells.
- *Keratoacanthoma* is a self-limiting tumour, which resembles clinically and histopathologically to well-differentiated squamous cell carcinoma.
- *Naevus cells* are cells of neural crest origin and have ability to produce melanin.
- *Junctional naevus:* Naevus cells are present only in the surface epithelium.
- *Compound naevus:* Naevus cells are present in both epithelium and connective tissue.
- *Intradermal or intramucosal naevus:* Naevus cells are present in the connective tissue.
- *Oral premalignant lesion* is a morphologically altered tissue in which cancer is more likely to occur than its apparently normal counterpart (leukoplakia, erythroplakia, palatal keratosis associated with reverse smoking and solar keratosis).
- *Oral precancerous condition* is a generalized state associated with a significantly increased risk of cancer (oral submucous fibrosis, lichen planus, syphilis, xeroderma pigmentosum, discoid lupus erythematosus and epidermolysis bullosa).
- *Mild epithelial dysplasia:* Dysplastic features involving the basal and parabasal layers.
- *Moderate epithelial dysplasia:* Dysplastic features involving from basal layer to the mid-portion of spinous layer.
- *Severe epithelial dysplasia:* Dysplastic features involving from basal layer to a level above the mid-portion of epithelium.
- *Carcinoma in situ* shows dysplastic features involving entire thickness of epithelium.
- *TNM clinical staging of oral squamous cell carcinoma:* Stage I—T1N0M0, Stage II—T2N0M0, Stage III—T3N0M0 and T1, T2, T3 with N1, M0 and Stage IV—Any T4 lesion, Any N2 or N3 lesion or M1 lesion.
- *ABCDE* rule for clinical diagnosis of melanoma: *A*symmetry of the lesion; *B*order irregularity with blurred, notched or ragged edges; *C*olour irregularity; *D*iameter will be greater than 6 mm and *E*levation of lesion.

- The *lipoma* is a benign tumour of fat tissue.
- *Syndromes associated with haemangiomas:* Rendu–Osler–Weber syndrome, Sturge–Weber syndrome, Kasabach–Merritt syndrome, Maffucci syndrome, von Hippel–Lindau syndrome, Klippel–Trenaunay syndrome.

- *Leiomyoma* is a benign neoplasm of smooth muscle.
- *Rhabdomyoma* is a benign neoplasm of skeletal muscle.
- *Leiomyosarcoma* is a malignant neoplasm of smooth muscle origin.
- *Rhabdomyosarcoma* is malignant neoplasm of skeletal muscle origin.
- *Fibrosarcoma* exhibits pleomorphic fibroblasts typically arranged in a herringbone or interlacing fascicular pattern.
- *Kaposi's sarcoma* is commonly associated with HIV/AIDS patients.
- *Ewing's sarcoma* is a highly malignant, small, round to oval cell sarcoma with the clinical and radiographic characteristics of a primary osseous lesion.
- *Osteosarcomas* arise from pre-existing bone abnormalities such as *Paget's disease, fibrous dysplasia, giant cell tumour, multiple osteochondromas, bone infarct, chronic osteomyelitis* and *osteogenesis imperfecta.*
- *Non-Hodgkin's lymphomas* are heterogenous group of lymphoproliferetion malignancies involving lymph nodes, lymphoid organs and extranodal organs.
- Reed–Sternberg (RS) cells are large malignant lymphoid cells seen in *Hodgkin's lymphoma.*
- *Malignant peripheral nerve sheath tumour* is a malignancy of Schwann cells.

Frequently asked questions

1. Squamous papilloma
2. Keratoacanthoma
3. Oral naevi/blue naevi
4. Potentially malignant disorders/premalignant lesions/premalignant conditions
5. Leukoplakia/epithelial dysplasia
6. Oral submucous fibrosis
7. Discuss pathogenesis, clinical features and histopathology of squamous cell carcinoma
8. TNM staging for oral carcinoma
9. Carcinoma of floor of mouth
10. Ackerman's tumours
11. Melanoma
12. Fibroma/peripheral ossifying fibroma/central ossifying fibroma/peripheral giant cell carcinoma/central giant cell granuloma
13. Lipoma

14. Hemangioma/Sturge–Weber syndrome
15. Rhabdomyoma/leiomyoma
16. Neurofibroma/von Recklinghausen disease/neurofibromatosis
17. Schwannoma
18. Fibrosarcoma
19. Liposarcoma
20. Kaposi's sarcoma
21. Ewing's sarcoma
22. Osteosarcoma
23. Non-Hodgkin's lymphoma
24. Burkitt's lymphoma
25. Hodgkin's lymphoma
26. Leiomyosarcoma/rhabdomyosarcoma

CHAPTER 3

Salivary gland pathology

Embryology of salivary gland

Salivary gland is an ectodermal structure, since it originates from the oral ectoderm. The process of formation of the glandular epithelium along with the ductal architecture is termed as *branching morphogenesis*. *Morphogenesis* means the determination of the shape of any structure which is determined by a combination of cell proliferation and cell movement. This is followed by the final encapsulation of the gland. The renewal of glandular structures is from reserve cells (stem cell pool) within the gland.

- **Major salivary glands**
 - In 6th to 8th weeks of intrauterine life, the phase of initiation occurs in all the major salivary glands (parotid, sublingual and submandibular glands).
 - The components of the mesoderm (e.g. lymphatics and lymph nodes) develop along with major salivary glands.
 - The encapsulation of glandular structure occurs in the later phases and thus the lymph nodes (i.e. cervical nodes) get encapsulated with the gland.
- **Minor salivary glands:** In the 10th week of intrauterine life, the phase of initiation starts in these glands and they all concentrate intraorally within the oral mucosa.

Cellular organization

For the description, normal histomorphology can be divided into two types of cells—*luminal* and *non-luminal (abluminal)*. Luminal cells include the *secretory acinar cells* and the *lining (luminal) ductal cells*. Abluminal cells include the *myoepithelial cells* and the *basal cells.* Proliferative capacity of the salivary gland epithelium was thought to be restricted to the *stem* or *reserve cells*, i.e. luminal and basal cells of intercalated and excretory ducts, respectively.

Pathogenesis of salivary gland tumours

Aetiology

- **Viruses:** Epstein–Barr virus (EBV) is shown to be strongly associated with pleomorphic adenomas but there is no convincing association between human salivary gland tumours and other viruses, including polyomavirus and papillomavirus.
- **Radiation**
 - The risk is directly related to the level of exposure to ionizing radiation.
 - There is a high frequency of both mucoepidermoid carcinomas and Warthin's tumours.
 - Therapeutic radiation, particularly of the head and neck region, has been linked with a significantly increased risk of developing salivary gland tumours.
- **Occupation:** Increased incidence of salivary gland carcinomas has been reported among workers in a variety of industries which include rubber, asbestos, arsenic, plumbing, automobile and cosmetics.
- **Lifestyle and nutrition:** No association between tobacco use and alcohol consumption and salivary gland cancers could be demonstrated. However, there is a strong association between smoking and Warthin's tumour.
- **Hormones**
 - Oestrogen receptors have been reported to be present in nearly 80% of normal glands in males and females. They have been reported in a minority of cases of acinic cell carcinoma, mucoepidermoid carcinoma and salivary duct carcinoma, but were not detected in adenoid cystic carcinoma. In some studies, oestrogen receptors have been reported to be present in pleomorphic adenomas but in others, oestrogen receptors were absent.
 - Progesterone receptors have been reported in normal salivary glands. They have been detected in a minority of pleomorphic adenomas, but high levels of expression were reported in recurrent pleomorphic adenomas.
 - Androgen receptors have been reported to be present in 90% of salivary duct carcinomas, carcinoma ex pleomorphic adenoma and basal cell adenocarcinoma.

Pathogenesis

Unicellular theory of origin

- The neoplasms arise from their adult differentiated counterparts of the salivary gland unit.

- Mucoepidermoid carcinomas and squamous cell carcinomas—excretory duct cells
- Oncocytic tumours—striated duct cells
- Acinic cell carcinomas—acinar cells
- Other adenomas and adenocarcinomas—intercalated duct cells

- This unicellular theory of origin was rejected on the fact that induction of neoplasm would require dedifferentiation of already specialized cells such as acinar and striated duct cells.

Semipleuripotential bicellular theory (Eversole, 1971)

- The basal cells are considered as reserve cells that function as stem cells, particularly for generation of duct luminal and acinar cells.
- The reserve cells remain confined to the basal cell layer of excretory and intercalated ducts.
- The reserve cells associated with intercalated duct cells are presumed to be responsible for replacement of intercalated ducts, striated ducts and acinar cells. Similarly, the reserve cells associated with the excretory duct give rise to the columnar and squamous cells of the excretory duct.

But, this theory was not accepted due to lack of specific evidence.

Multicellular histogenetic theory (Dardick, 1991)

- The luminal epithelial cells with mitotic figures are present at all levels of the ductal system. Under certain circumstances like duct obstruction and chronic sialadenitis, luminal cells in the excretory duct can undergo squamous, goblet and ciliated cell metaplasia. Similarly, the acinar cells are capable of dedifferentiation to duct-like cells and squamous metaplasia.

This suggests that any of the cells found in the normal salivary ductal system could probably serve as a precursor for neoplasia.

Tumour Progression in Salivary Gland Tumours

Tumour progression is a multistep process, which often involves sequential accumulation of genetic changes. Salivary gland tumours can progress in one of the following ways:

- Malignant transformation of benign salivary gland tumours (e.g. pleomorphic adenoma to carcinoma ex pleomorphic adenoma; basal cell adenoma to basal cell adenocarcinoma; myoepithelioma to myoepithelial carcinoma; oncocytoma to oncocytic carcinoma).
- Progression from low grade to high grade carcinoma (e.g. epithelial–myoepithelial carcinoma progresses to myoepithelial carcinoma).
- Dedifferentiation of a carcinoma to high grade carcinoma with loss of

original line of differentiation.
- Stromal invasion.

Classification of salivary gland diseases/salivary gland neoplasms

Classification of salivary gland diseases

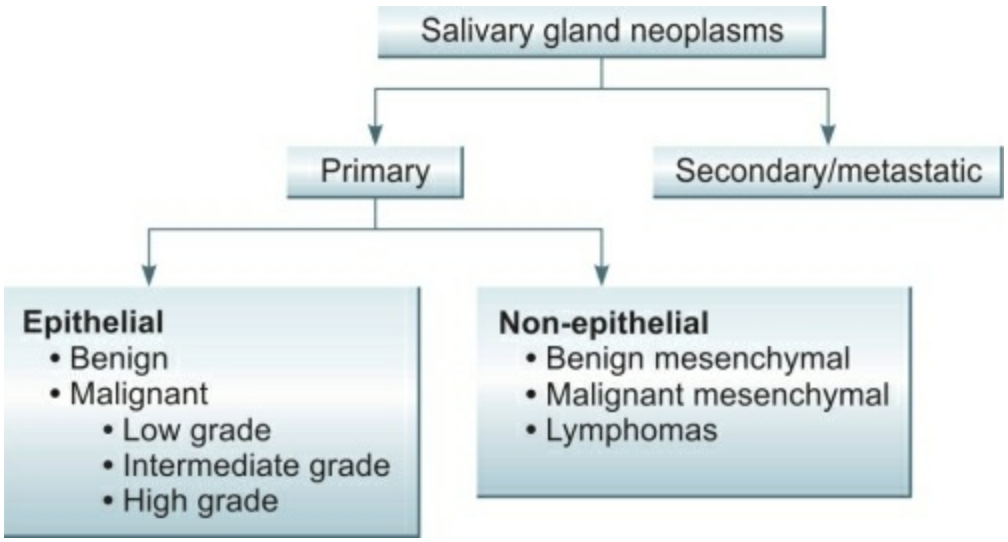
- **Developmental diseases**
 - Salivary gland aplasia
 - Salivary ductal atresia
 - Accessory parotid glands
 - Adenomatoid hyperplasia of salivary glands
 - Oncocytosis
 - Polycystic disease of parotid glands
- **Obstructive disorders**
 - Mucous extravasation phenomenon
 - Ranula
 - Mucous retention cyst
 - Sialolithiasis
- **Inflammatory and infectious diseases**
 - ***Sialadenitis***
 - Bacterial (suppurative)
 - Tuberculosis
 - Cat scratch disease
 - Sarcoidosis
 - ***Viral (nonsuppurative)***
 - Mumps
 - Cytomegalovirus (CMV) infection
 - Associated with AIDS
 - EBV infection
 - Parainfluenza type 1, 3 infection
 - ***Juvenile recurrent sialadenitis***
 - ***Radiation induced***
 - ***Electrolyte disturbances (cystic fibrosis)***
 - ***Chronic sclerosing sialadenitis (Kuttner's disease)***
 - ***Immune sialadenitis***
- **Functional disorders**

- Sialorrhoea
- Xerostomia

- **Immunologic diseases**
 - Benign lymphoepithelial lesion
 - Sjögren's syndrome
 - Allergic/immune sialadenitis
- **Idiopathic diseases**
 - Necrotizing sialometaplasia
 - Benign cysts of parotid glands
 - Angiolymphoid hyperplasia with eosinophilia
 - Kimura's disease
 - Cheilitis glandularis
- **Associated with systemic diseases**
 - ***Sialadenosis***
 - Hormonal
 - Diabetic sialosis
 - Alcoholic cirrhosis
 - Malnutrition
 - Deprivation

Classification of salivary gland neoplasms (WHO, 2005)

Salivary gland neoplasms are classified as shown in Flowchart 3.1.



FLOWCHART 3.1 Classification of salivary gland neoplasms

Primary epithelial neoplasms

Benign neoplasms

- Pleomorphic adenoma
- Warthin's tumour
- Oncocytoma
- Cystadenoma
- Basal cell adenoma
- Canalicular adenoma
- Ductal papillomas
- Inverted ductal papilloma
- Intraductal papilloma
- Sialadenoma papilliferum
- Myoepithelioma
- Sebaceous adenoma
- Adenoma, not otherwise specified

Malignant neoplasms

- *Low grade*
 - Mucoepidermoid carcinoma, low grade
 - Acinic cell adenocarcinoma
 - Polymorphous low grade adenocarcinoma
 - Basal cell adenocarcinoma
 - Adenocarcinoma, not otherwise specified, low grade
 - Metastasizing mixed tumour
- *Intermediate grade*
 - Mucoepidermoid carcinoma, intermediate grade
 - Adenoid cystic carcinoma, cribriform–tubular
 - Epithelial–myoepithelial carcinoma
 - Adenocarcinoma, not otherwise specified, intermediate grade
 - Clear cell carcinoma
 - Cystadenocarcinoma
 - Sebaceous carcinoma
 - Mucinous adenocarcinoma
- *High grade*
 - Mucoepidermoid carcinoma, high grade
 - Adenoid cystic carcinoma, solid
 - Malignant mixed tumours
 - Carcinoma ex pleomorphic adenoma
 - Carcinosarcoma

- Adenocarcinoma, not otherwise specified, high grade
- Squamous cell carcinoma
- Undifferentiated carcinomas
 - Small cell carcinoma
 - Malignant lymphoepithelial lesion
 - Others
- Oncocytic carcinoma
- Adenosquamous carcinoma
- Salivary duct carcinoma
- Myoepithelial carcinoma

Primary non-epithelial neoplasms

- **Benign mesenchymal neoplasms**
 - Haemangioma
 - Schwannoma
 - Neurofibroma
 - Lipoma
 - Others
- **Malignant mesenchymal neoplasms (sarcomas)**
 - Haemangiopericytoma
 - Malignant schwannoma
 - Fibrosarcoma
 - Malignant fibrous histiocytoma
 - Rhabdomyosarcoma
 - Others
- **Lymphomas**
 - Non-Hodgkin's disease
 - Hodgkin's disease

Metastatic neoplasms

- Malignant melanoma
- Squamous cell carcinoma
- Renal cell carcinoma
- Thyroid carcinoma
- Others

Benign tumours of salivary glands

Pleomorphic adenoma

(*Synonym: Benign mixed tumour*)

- The most common benign salivary neoplasm consisting of cells exhibiting the ability to differentiate epithelial cells (ductal and nonductal—myoepithelial) and mesenchyme-like cells (chondroid, myxoid and osseous). This results in different histopathologic patterns (spectrum) in these tumours, hence the name *pleo*—many and *morphic*—size, shape or form for the tumour tissue.
- The synonym *benign mixed tumour* is a misnomer, as it is only ectodermal, i.e. epithelial in origin. The other germ layers are not involved, but it has features of mixed tumours.

Pathogenesis

Histopathologically, the presence of both epithelial and mesenchymal elements had raised a lot of controversy regarding the pathogenesis of this tumour. The various theories put forth to explain the pathogenesis of pleomorphic adenoma are as follows:

- The early German school of thought suggests that it simultaneously arises from epithelial and mesenchymal components which correspond to the concept of mixed tumour.
- The French school of thought suggests that the tumour is exclusively derived from epithelium and develops from mature salivary tissue, whereas the mesenchymal components are the result of stromal metaplasia occurring as a result of chemical influences which is secreted by epithelial tumour cells.
- The present and most accepted theory suggests that the tumour has a concomitant origin from epithelial and myoepithelial cells. This concept is supported by various immunohistochemical and ultrastructural investigations. The epithelial components are thought to be derived from luminal cells whereas mesenchymal components are from the myoepithelial cells.

Clinical features

- **Age.** 30–50 years.
- **Gender.** Female predilection.

- **Location.** Superficial lobe of parotid gland is most commonly affected and among the minor salivary glands, the posterior lateral palatal glands are affected.
- **Signs and symptoms**
 - It is a slow-growing and painless mass.
 - When the superficial lobe of parotid is involved, the ear lobe is elevated.
 - On palpation, it is firm in consistency.
 - Major salivary gland tumours can grow to a large size; when they enlarge, they are immovable.
 - Pain and facial nerve palsy are rare findings; they are commonly associated with malignant lesions.
 - Palatal tumours are smooth-surfaced and dome-shaped masses.

Histopathology (fig. 3.1)

- Well-circumscribed, encapsulated tumour and sometimes the tumour cells infiltrate the capsule.
- Foote and Frazell (1954) categorized tumour into following types:
 1. Principally myxoid
 2. Myxoid and cellular components in equal proportion
 3. Predominantly cellular
 4. Extremely cellular
- It is comprised of three main components:
 1. Epithelial component (glandular epithelium)
 2. Myoepithelial cells
 3. Connective tissue stroma (mesenchyme-like)

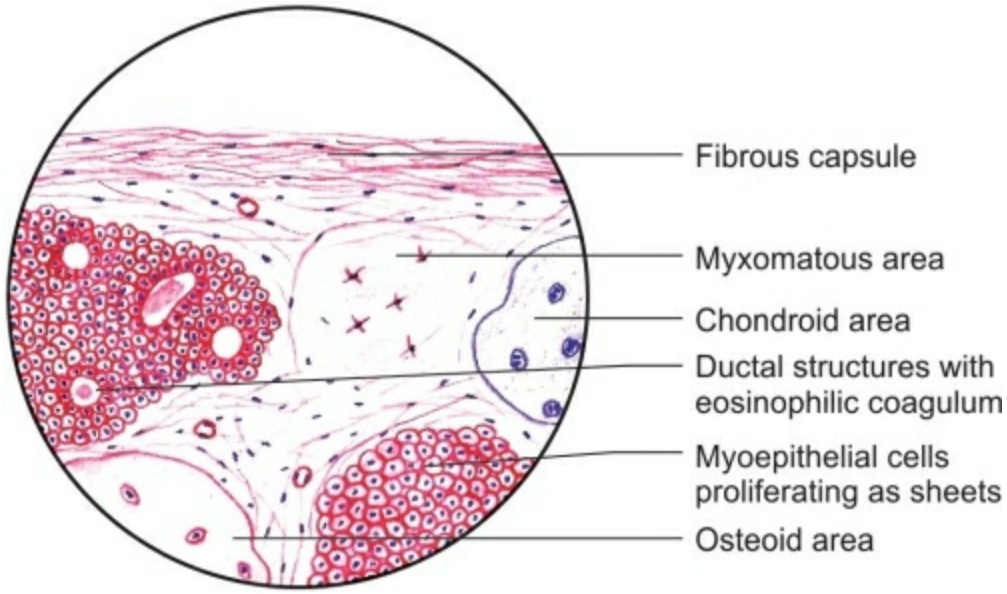


FIG. 3.1 Pleomorphic adenoma.

Epithelial component

- It occurs as small cellular nests, sheets, anatomizing cords and foci of keratinizing squamous or spindle cells.
- It forms ducts and small cysts that may contain eosinophilic coagulum.

Myoepithelial cells

- They form a major component of tumour.
- They appear as polygonal-, spindle-, angular- or plasmacytoid-shaped cells.
- Plasmacytoid myoepithelial cells: *Plasma cell like,* round- to oval-shaped cells with an eccentrically placed nucleus and eosinophilic cytoplasm.
- Hyaline cells: Some cells are round in shape with eccentric nuclei and hyalinized eosinophilic cytoplasm.
- Myoepithelial cells show mesenchymal changes with extensive accumulation of mucoid material around individual cells—myxoid appearance.
- Vacuolar degeneration of myoepithelial cells—cartilaginous appearance.
- If myoepithelial proliferation predominant—myoepithelioma.

Connective tissue stroma

- Accumulation of mucoid material between tumour cells is commonly seen.
- Chondroid, osteoid, myxoid areas help in diagnosis of pleomorphic adenoma.

Differential diagnosis

- Adenolymphoma
- Oncocytoma
- Adenocarcinoma

Prognosis and predictive factors

- Surgical excision is the best treatment. Since these tumours are radio-resistant, the use of radiation therapy is not benefited.
- Rarely, malignant changes may occur—carcinoma ex pleomorphic adenoma, metastasizing benign mixed tumour.
- Recurrence is very rare.

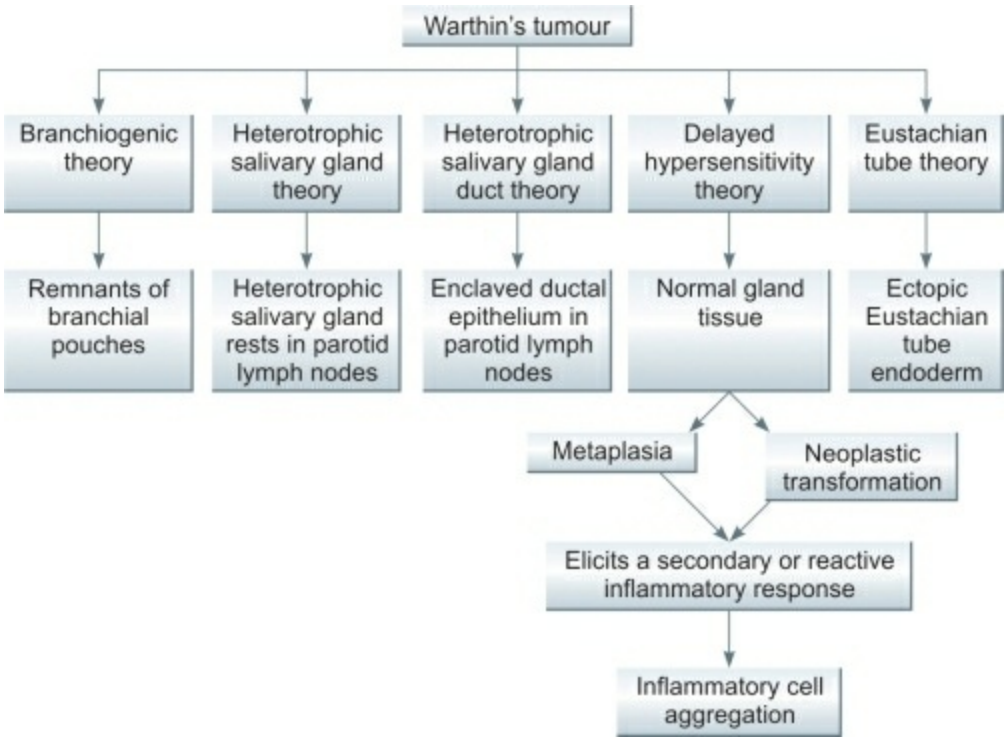
Warthin's tumour

(Synonyms: Papillary cystadenoma lymphomatosum; adenolymphoma)

- It is the second most common benign salivary neoplasm characterized by proliferation of both luminal and non-luminal cells.

Pathogenesis (flowchart 3.2)

Some studies showed a strong association between cigarette smoking and Warthin's tumour. The exact mechanisms are not clear but it is speculated that irritants in tobacco smoke cause metaplasia in the parotid gland.



FLOWCHART 3.2 Pathogenesis of Warthin's tumour

Clinical features

- **Age.** 60–70 years.
- **Gender.** Male predilection, but some recent studies demonstrate female predilection also. This change in sex ratio may reflect the increased prevalence of smoking in women.
- **Location.** Parotid gland is most commonly affected.
- **Signs and symptoms**
 - It appears as a slow-growing, painless nodular mass.
 - On palpation, it is firm in consistency or fluctuant.
 - It can occur as a bilateral lesion (unique feature of Warthin's tumour).

Most of these tumours do not occur simultaneously, but are metachronous (occurring at different times). The association of smoking may also help to explain the bilaterality of the tumour, because any tumourigenic effects of smoking might be manifested in both parotids.

Histopathology (fig. 3.2)

- The lesion exhibits cyst formation with papillary projections into the cystic spaces and a lymphoid matrix showing germinal centres.
- The cysts are lined by papillary proliferations of bilayered oncocytic epithelium:

- Inner luminal layer cells are tall columnar with centrally placed, palisaded, hyperchromatic nuclei and fine granular, eosinophilic cytoplasm.
- Outer layer cells are cuboidal or polygonal cells with more vesicular nuclei.
- Eosinophilic coagulum is commonly present within cystic spaces.

- Lining epithelium shows multiple papillary infoldings that protrude into the cystic spaces.
- Epithelium is supported by lymphoid stroma. The abundant lymphoid components may represent the normal lymphoid tissue of lymph node which involves both humoral and cell-mediated mechanisms.

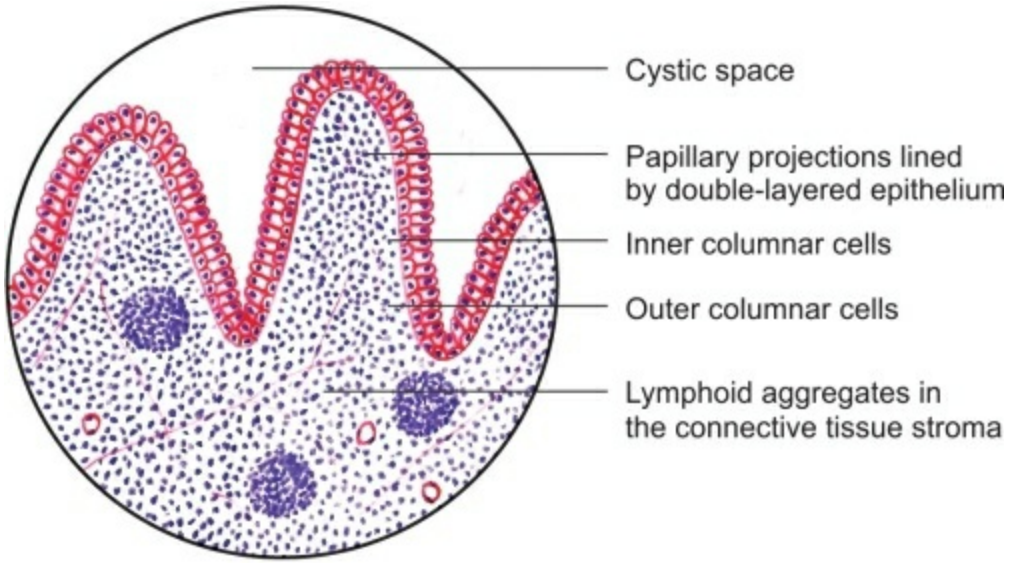


FIG. 3.2 Warthin's tumour.

Differential diagnosis

- Pleomorphic adenoma
- Oncocytoma
- Parotid lymph node enlargement

Prognosis and predictive factors

- Surgical excision is advised.
- Malignancy associated with Warthin's tumour is very rare.
- Recurrence is rare.

Oncocytoma

(Synonyms: Oncocytic adenoma; oxyphilic adenoma; acidophilic adenoma)
It is a benign salivary gland tumour composed of oncocytes (large cells with prominent eosinophilic granular cytoplasm). The name *oncocytes* is derived from the resemblance of these tumour cells to apparently normal cells. *Oncocytes* are found usually in salivary glands, respiratory tract, breast, thyroid, pancreas, parathyroid, pituitary, testicle, fallopian tube, liver and stomach.

Pathogenesis

- Oncocytic cells are considered as somatic mutants, rather than as a new or specific cell lineage. They represent acini or intralobular ducts of normal or abnormal salivary tissues which have undergone cytoplasmic changes induced by unknown cause.
- Oncocytic transformation of the epithelial cells is not a degenerative process, but rather is considered as a redifferentiation of the epithelial cells which develop an increased but unbalanced metabolism.

Clinical features

- **Age.** 50–80 years.
- **Gender.** Female predilection.
- **Location.** Parotid gland is most commonly involved.
- **Signs and symptoms**
 - It appears as a discrete, encapsulated, slow growing mass.
 - The tumour usually measures 3–5 cm in diameter.
 - Generally, it will be painless and firm in consistency.
 - Diffuse multinodular oncocytoma or oncocytosis appears when many nodular masses involve the entire salivary gland.

Histopathology

- It is a well-encapsulated tumour composed of oncocytes.
- Oncocytes are large cells with prominent eosinophilic granular cytoplasm with a centrally place nuclei.
- Oncocytes are arranged in sheets, nests or cords. Rarely, an alveolar or glandular pattern of oncocytes is also seen.
- The granularity in cytoplasm is due to presence of mitochondria, which can be identified in light microscope using a special stain *—phosphotungstic acid haematoxylin (PTAH) stain.*

- Oncocytes with clear cytoplasm (glycogen-rich cytoplasm) are rarely seen.
- ***Ultrastructural features***
 - Oncocyte is a cytoplasmic volume packed with mitochondria to the exclusion of most other organelles.
 - Oncocytic cell mitochondria vary in size and shape from 0.2 to 5 μm, swollen, spherical forms with long, interdigitating cristae and varying degree of pleomorphism.

Differential diagnosis

- Pleomorphic adenoma
- Warthin's tumour
- Parotid lymph node enlargement

Prognosis and predictive factors

- It is best treated by surgical excision.
- Oncocytoma of minor salivary gland involvement should be removed with small margin of normal surrounding tissue.
- The prognosis after removal is good with a low rate of recurrence.
- Rarely, malignant transformation may occur *(oncocytic carcinoma).*

Basal cell adenoma

It is an uncommon salivary gland neoplasm, histopathologically composed of basaloid (resembling basal cells) epithelial cells (hence the name basal cell adenoma) arranged in solid, trabecular, tubular or membranous patterns.

Pathogenesis

- Basal cell adenoma arises from neoplastic transformation of the reserve cells in the intercalated duct with histodifferentiation towards ductal and myoepithelial differentiation.
- It shows differentiation of both epithelial and myoepithelial elements.

Clinical features

- **Age.** 50–70 years.
- **Gender.** Female predilection.
- **Location.** Parotid gland is most commonly affected.
- **Signs and symptoms**
 - It appears slowly growing, freely movable and painless mass.
 - Most of the tumours are less than 3 cm in diameter.

Histopathology

- It is a well-encapsulated tumour in major salivary glands, whereas in minor salivary glands, the capsule will be ill-defined.
- Two cell types are seen:
 1. Basaloid cells: Small cells with prominent nucleus and scanty cytoplasm.
 2. Large cells with prominent eosinophilic cytoplasm and pale staining nuclei.
- Four histopathological forms are seen:
 1. *Solid type:* It a most common variant. It consists of basaloid cells in the form of broad islands and cords that are supported by a fibrous stroma.
 2. *Tubular type:* This pattern exhibits multiple duct- or tubule-like structures that are lined by inner cuboidal cells and outer basaloid type cells.
 3. *Trabecular type:* It shows epithelial islands, which are narrower and cord-like, and are interconnected producing reticular pattern.
 4. *Membranous type:* It exhibits multiple large lobules molded in the form of jigsaw puzzle fashion. These lobules are surrounded by hyaline material, which represents reduplication of basement membrane.

Differential diagnosis

- Canalicular adenoma
- Sebaceous adenoma
- Clear cell adenoma

Prognosis and predictive factors

- Surgical excision.
- Recurrence is rare.

Canalicular adenoma

It is an uncommon neoplasm composed of columnar epithelial cells arranged in a single or double layer forming branching cords in a loose stroma.

Pathogenesis

Canalicular adenoma arises from neoplastic transformation of the reserve cells in the intercalated duct with histodifferentiation towards ductal cells

with none to very minimal myoepithelial differentiation.

Clinical features

- **Age.** 35–70 years.
- **Gender.** Female predilection.
- **Location.** Commonly occurs in minor salivary glands of upper lip and buccal mucosa.
- **Signs and symptoms**
 - It manifests as well-circumscribed, slow growing, painless mass that usually ranges from several millimetres to 2 cm.
 - It may be firm or fluctuant to palpation.

Histopathology

- It is composed of long columns or cords of cuboidal or columnar cells in a single layer.
- These single layers of cells are parallel, forming long canals.
- Sometimes, row of cells are closely approximated and appear as a double row of cells showing a *party wall*.
- The cystic spaces are usually filled with an eosinophilic coagulum.

Differential diagnosis

- Basal cell adenoma
- Sebaceous adenoma
- Clear cell adenoma

Prognosis and predictive factors

- Surgical excision.
- Recurrence is rare.

Ductal papillomas

They include three rare benign salivary gland neoplasms which exhibit papillary projections (i.e. showing surface projections), histopathologically. The unique features to these tumours are:

- Papillary projections.
- All three tumours arise from the excretory duct.
- Commonly affect the minor salivary gland.

Three benign tumours of this group include:

1. Intraductal papilloma

2. Sialadenoma papilliferum
3. Inverted ductal papilloma

Pathogenesis

- The possible cell of origin has been variously reported as the excretory duct reserve cell, intercalated duct cells or striated duct cells.
- Based on the location of the tumour, it seems that the salivary gland excretory duct cell is the possible cell of origin.

Intraductal papilloma

It shows luminal papillary proliferation of the interlobular or excretory duct and forms a single cystic dilated mass.

Clinical features

- **Age.** 30–60 years.
- **Gender.** No sex predilection.
- **Location.** Most common in minor salivary glands of lower lip and buccal mucosa.
- **Signs and symptoms:** It occurs as firm, discrete, asymptomatic submucosal masses usually ranging up to 2 cm in dimension.

Histopathology

- It is an encapsulated lesion within a single cystic cavity.
- Cavity is filled with papillomatous masses.
- Papilla is lined by cuboidal to columnar epithelial cells and consists of a connective tissue core.

Prognosis and predictive factors

- Surgical excision.
- Recurrence is rare.

Sialadenoma papilliferum

It is an exophytic tumour with multiple papillary surface folds and deeper duct-like structures that are usually in continuity with the surface epithelium.

Clinical features

- **Age.** 30–70 years.
- **Gender.** Male predilection.
- **Location.** Most commonly in minor glands of palate and buccal mucosa.
- **Signs and symptoms**
 - It usually occurs near or at the orifice of a salivary gland excretory duct.
 - It presents as a well-circumscribed, painless, papillary exophytic growth.

Histopathology

- This tumour is composed of both exophytic and endophytic components.
- The outer exophytic portion:
 - Broad-based finger-like projections supported with delicate fibrous connective tissue cores extending above the level of adjacent mucosa.
 - The covering epithelium of the folds is stratified squamous which may be hyperkeratotic or parakeratotic.
 - A mixed inflammatory cell infiltrate, composed of lymphocytes, plasma cells and neutrophils, is present.
- The deeper endophytic portion:
 - It is unencapsulated and composed of glands or branching occasionally tortuous ducts that may be cystic and are continuous with interpapillary clefts of surface component.
 - The epithelium lining of ducts and cysts is usually composed of double layer of cells, a tall columnar luminal cell layer and a cuboidal or flattened basal cell layer.
 - Both cell types are brightly eosinophilic with oncocytic features and are consistent with interlobular and excretory duct epithelium.

Prognosis and predictive factors

- Surgical excision.
- Recurrence is rare.

Inverted ductal papilloma

It is rarest of the three types of ductal papillomas.

Clinical features

- **Age.** 30–80 years.
- **Gender.** Male predilection.
- **Location.** Minor salivary gland of lower lip, buccal mucosa and vestibule of

lower jaw.

- **Signs and symptoms**
 - It manifests as an asymptomatic, firm, submucosal nodule and does not exceed 1.5 cm in diameter.
 - It occurs near the orifice of salivary ducts.

Histopathology

- It is a well-demarcated endophytic epithelial mass with a punctum on mucosal surface.
- It is composed of basaloid and stratified squamous epithelium usually without keratin surrounding fibrovascular cores extending in a broad, bulbous papillary pattern from a luminal surface and usually filling the lumen.
- Usually, cleft-like spaces between papillary folds may be seen.
- Occasionally, mucous cells may also be seen.

Prognosis and predictive factors

- Surgical excision.
- Recurrence is rare.

Malignant tumours of salivary glands

Mucoepidermoid carcinoma

(Synonyms: Mixed epidermoid; mucus-secreting carcinoma)

Mucoepidermoid carcinoma is a malignant salivary gland tumour, which is characterized histopathologically by the presence of three cell types: mucous cells, intermediate cells (with a basaloid pattern) and epidermoid cells (squamous cell-like) and hence the name.

It is the most common malignant salivary gland tumour in major and minor salivary glands among children and adults.

Pathogenesis

- Mucoepidermoid carcinomas are thought to arise from the excretory duct cells.
- Excretory ducts are structures devoid of myoepithelial cells, hence mucoepidermoid carcinomas are derived from a single parent cell, probably the basal cells of the excretory duct that undergoes luminal and myoepithelial differentiation.
 - *Luminal cells*—cuboidal cells, goblet cells, clear cells and squamoid cells.
 - *Myoepithelial abluminal cells*—myoepithelial cells, intermediate cells, clear cells and squamoid cells.

Clinical features

- **Age.** 20–50 years.
- **Gender.** Female predilection.
- **Location**
 - Major salivary gland—parotid gland.
 - Minor salivary gland—palate, buccal mucosa, tongue and retromolar pad.
- **Signs and symptoms**
 - Tumours of low-grade malignancy
 - Slowly enlarging, painless mass seldom exceed 5 cm in diameter.
 - These are not completely encapsulated and often contain cystic cavities which may be filled with a viscid, mucoid material.
 - Tumour of high-grade malignancy
 - Rapidly grow and produce pain as an early symptom.
 - Facial paralysis is frequently seen.

- Patient may also complain of trismus, drainage from ear, dysphagia, numbness of adjacent area and ulceration, especially in tumours of minor salivary glands.
- These are unencapsulated lesions, so they tend to infiltrate the surrounding tissue.
- Many cases show metastasis to regional lymph nodes. Distant metastases to lung, bone, brain and subcutaneous tissues are also common.

Radiographic features

Cortical bone resorption will be evident.

Histopathology (fig. 3.3)

- Mucoepidermoid carcinomas are characterized histologically by the presence of a variety of cell types and growth patterns.
- Usually, tumour may contain mucous, epidermoid and intermediate cells. Sometimes even columnar or clear cells are seen. Each cell proliferates alone or in many different combinations in a cystic or solid pattern.
- **Mucous cells**
 - These have abundant, pale, foamy cytoplasm and are relatively large in size, which may assume round, cuboidal, ovoid, columnar or goblet shapes.
 - These cells often occur in small clusters or line cystic spaces into which mucin is deposited.
 - In high-grade lesions, mucous cells are scattered singly in vast number.
- **Intermediate cells**
 - These are intermediate in size and appear between mucous and epidermoid cells.
 - These demonstrate gradual transition in sizes from small basal cells (slightly larger than lymphocytes and have little to no discernible cytoplasm) to cells having a wide rim of cytoplasm.
 - The smaller basal cells are usually seen in cluster and have capacity to further differentiate to epidermoid, mucous or clear cells.
 - The cytoplasmic borders of intermediate cells are sharply demarcated notably so in areas where cells are less cohesive; however, often the cells have a more syncytial arrangement in which individual borders are difficult to appreciate.
- **Epidermoid cells:** These are characterized by squamoid features—

polygonal shape, intercellular bridges and rarely keratinization.

- **Clear cells**
 - Cells are large and polygonal in shape. They have sharply defined cytoplasmic borders with clear cytoplasm.
 - Usually, these cells contain abundant, demonstrable mucin but in most clear cells, only traces are seen focally.
- Mucoepidermoid carcinomas have been categorized into three histologic grades based on the following:
 - Amount of cyst formation
 - Degree of cytologic atypia
 - Relative numbers of mucous, epidermoid and intermediate cells.
- *Low-grade tumours:* These show well-formed glandular structures and prominent mucin filled cystic spaces, minimal cellular atypia and high proportion of mucous cells.
- *Intermediate-grade tumours*
 - These show solid areas of epidermoid cells and intermediate cells.
 - Cyst formation is seen but is less prominent than that observed in low-grade tumours.
 - All cell types are present, but intermediate cells will be prominent.
 - Cellular atypia may or may not be observed.
- *High-grade tumours*
 - These consist of cells present as solid nests and cords of intermediate cells and epidermoid cells.
 - Prominent nuclear pleomorphism and mitotic activity are noted.
 - Cystic component is usually very less (<20%).
 - Glandular component is rare.
 - Necrosis and perineural invasion may be present.
- However, some authors have found that the relative proportion of three different cell types does not necessarily correlate the prognosis. To overcome this, two expert groups have proposed evaluation schemes based on significant microscopic parameters, to which the relative point values have been assigned to determine the grade of the tumour
 - *Auclair et al (1992)*

Histopathologic feature	Points
Cystic component <20%	2
Neural invasion	2
Necrosis	3
Four or more mitoses per 10 high power fields	3
Anaplasia	4
Tumour grade	**Point score**
Low	0–4
Moderate	5–6
Severe	7 or more

- *Brandwein et al (2001)*

Histopathologic feature	Points
Cystic component <25%	2
Tumour front invades in small nests and islands	2
Pronounced nuclear atypia	2
Lymphatic or vascular invasion	3
Bone invasion	3
Four or more mitoses per 10 high power fields	3
Perineural spread	3
Tumour grade	**Point score**
I	0
II	2–3
III	4 or more

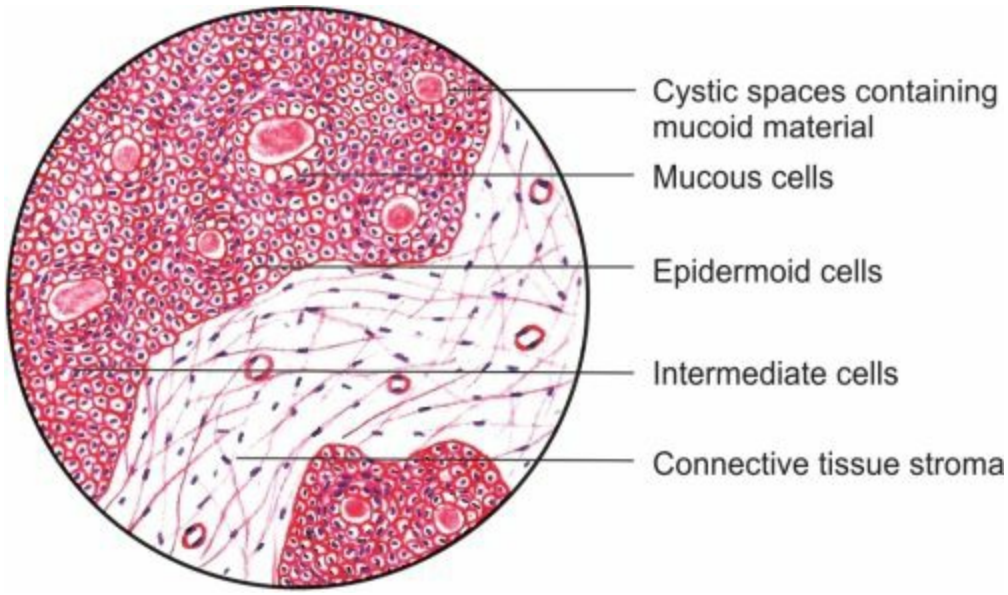


FIG. 3.3 Mucoepidermoid carcinoma.

Differential diagnosis

- Necrotizing sialometaplasia
- Adenosquamous cell carcinoma
- Pleomorphic adenoma

Prognosis and predictive factors

- Conservative excision with preservation of the facial nerve is recommended for low- and intermediate-grade tumours, whereas complete excision is recommended for high-grade tumours.
- Few investigators recommend radiotherapy and chemotherapy for high-grade tumours.
- Low-grade tumours have a 5-year cure rate of 92%, whereas the intermediate and high-grade tumours have 49% 5-year cure rate.

Adenoid cystic carcinoma

(Synonyms: Cylindroma; adenocystic basal cell carcinoma; basaloid mixed tumour)
It is a slow-growing but aggressive neoplasm with a remarkable capacity for recurrence. The term *cylindroma* should be avoided because it does not convey the malignant nature of the tumour and also because the same term is used for a skin adnexal tumour that has a markedly different clinical presentation and diagnosis.

Pathogenesis

Adenoid cystic carcinoma is thought to arise from the neoplastic transformation of reserve cells of the terminal duct system. These neoplastic cells differentiate along the lines of ductal or myoepithelial cells.

Clinical features

- **Age.** 50–60 years. (It is rare in younger age group.)
- **Gender.** Female predilection.
- **Location.** Minor salivary glands of palate, submandibular and parotid salivary gland.
- **Signs and symptoms**
 - It appears as a slow-growing mass.
 - Pain may be evident even before a visible swelling due to perineural invasion. Patient often complains of constant, low grade, dull ache, which is gradually an increase in intensity.

- Nerve paralysis (facial nerve, if parotid gland is involved) is a common finding like any other malignant tumour.
- Invasion into the surrounding structures is also evident.
- Palatal tumours can be smooth-surfaced or ulcerated.

Note: Adenoid cystic carcinoma has marked tendency to spread through perineural spaces and usually invades well beyond the clinically apparent borders, so pain is a typical feature in this tumour.

Perineural invasion is not pathognomonic for adenoid cystic carcinoma, it is also seen in other salivary gland malignancies like *polymorphous low-grade adenocarcinoma (PLGA).*

Radiographic features

Palatal tumours cause erosion of underlying bone and infiltrate into the nasal cavity or maxillary sinus.

Histopathology (fig. 3.4)

- It is composed of mixture of ductal cells and myoepithelial cells that can have a varied arrangement.
- Three major patterns are recognized:
 1. Cribriform
 2. Tubular
 3. Solid

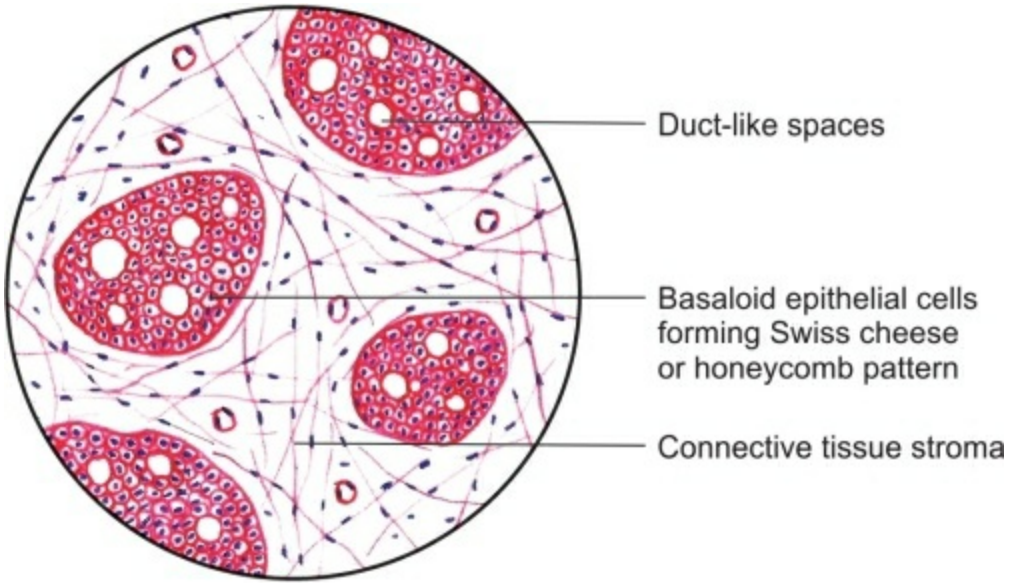


FIG. 3.4 Adenoid cystic carcinoma.

Usually combination of these is seen, pure forms are very rare. The tumour is categorized based on the predominant pattern.

- *Cribriform pattern*
 - It consists of islands of basaloid (basal cell-like) epithelial cells containing multiple cylindrical, cyst-like spaces resembling *Swiss cheese* or *honey comb pattern.*
 - Cystic spaces contain a basophilic mucoid material, hyalinized eosinophilic product or combined of mucoid with hyalinized appearance.
 - Tumour cells are small and cuboidal exhibiting deeply basophilic nuclei and little cytoplasm.

Note: PLGA also exhibits areas with cribriform pattern.

- *Tubular pattern*
 - It consists of multiple small ducts or tubules within a hyalinized stroma.
 - The tubular lamina is lined by one or several layers of cells. Sometimes, both layers of ductal cells and myoepithelial cells can be seen.
- *Solid variant*
 - It consists of islands or sheets of tumour cells that demonstrate little

tendency towards duct or cyst formation.
- Cellular pleomorphism and mitotic activity as well as focal necrosis in the centre of the tumour islands may be seen.

Differential diagnosis

- Polymorphous low-grade adenocarcinoma
- Epithelial myoepithelial carcinoma
- Adenocarcinoma

Prognosis and predictive factors

- Wide local and radical surgical excision with or without postoperative radiation is the treatment of choice.
- Radiation alone or with chemotherapy can be instituted for recurrent or metastatic tumours.
- Prognosis depends on the histological patterns, tumour site, clinical stage and bone involvement.
- Solid variant of adenoid cystic carcinoma has a bad prognosis compared to other variants.

Polymorphous low-grade carcinoma (PLGA)

(Synonyms: Lobular carcinoma; terminal duct carcinoma; trabecular carcinoma; papillary carcinoma)

It is a malignant salivary gland tumour that is essentially limited in occurrence to minor salivary glands and histopathologically has many growth patterns, bland and has an infiltrative and low metastatic potential, hence the name *polymorphous low-grade carcinoma*.

It is the second most common malignancy affecting the minor salivary glands, i.e. after mucoepidermoid carcinoma.

Pathogenesis

Polymorphous low-grade adenocarcinoma is thought to arise from the neoplastic transformation of reserve cells of the terminal duct system. These neoplastic cells differentiate mainly along the lines of ductal cells with a limited potential to differentiate along lines of myoepithelial cells.

Clinical features

- **Age.** 50–80 years.
- **Gender.** Female predilection.

- **Location.** Minor salivary glands of hard and soft palate, buccal mucosa and upper lip.
- **Signs and symptoms**
 - It presents as a firm, non-tender, slow-growing, long duration swelling involving the mucosa.
 - Discomfort, bleeding, telangiectasia or ulceration of the overlying mucosa may occasionally occur.
 - Tumour can erode or infiltrate the underlying bone.

Histopathology

- The tumour cells have cytologic uniformity and histologic blandness.
- The cells are cuboidal or columnar in shape with indistinct cell borders and pale to eosinophilic cytoplasm. The nuclei may be round, ovoid or spindle shape.
- The tumour cells may show polymorphic growth patterns like solid, ductal, cystic and tubular patterns, hence the name *polymorphous.*
- The peripheral cells are usually infiltrative, invading the adjacent tissue in a *single file fashion* or *Indian file fashion.*
- The stroma is often mucoid in nature or it may demonstrate hyalinization.
- Perineural invasion is also a common feature that mimics adenoid cystic carcinoma.

Note: Distinction between adenoid cystic carcinoma and PLGA is important because of their different prognosis. Adenoid cystic carcinoma is more prone to recurrence and distinct metastasis, whereas PLGA rarely recur and show distinct metastasis (Table 3.1).

Table 3.1

Comparison between adenoid cystic carcinoma and PLGA

Adenoid cystic carcinoma	PLGA
Myoepithelial cells—more	Myoepithelial cells—less
Ductal cells—less	Ductal cells—more
High recurrence	Less recurrence
Less metastasis—bone erosion is rare	High metastasis—bone erosion is common
CD43, CD117—positive	CD43, CD117—negative
GFAP—positive	GFAP—negative

Differential diagnosis

- Adenoid cystic carcinoma
- Pleomorphic adenoma
- Adenocarcinoma

Prognosis and predictive factors

- Conservative wide surgical excision is advised.
- Prognosis is good, it is not influenced by perineural invasion.
- Recurrence is common but metastasis does not occur.

Acinic cell carcinoma

(Synonyms: Acinic cell; serous cell adenocarcinoma)

It is a malignant salivary gland neoplasm in which the neoplastic cells express acinar differentiation, hence the term *acinic cell carcinoma*.

Pathogenesis

- Acinic cell carcinoma arises from neoplastic transformation of the reserve cells in the intercalated duct cells with histodifferentiation into serous acinar cells.
- The varying patterns of differentiation seen in acinic cell carcinomas are attributed to the attempt of the terminal tubule or intercalated duct reserve cells to simulate the neoplastic equivalent of the normal phenotypic expression of lobules of acini.
- The complete expression of this differentiation of these neoplastic cells results in the classically defined acinic cell carcinomas (lobules of acini).
- Those acinic cell carcinomas with imperfect differentiation retain areas of tubular or solid epithelial masses.

Clinical features

- **Age.** 20–70 years, even age distribution.
- **Gender.** Female predilection.
- **Location.** Parotid salivary gland followed by minor salivary glands of lips and buccal mucosa.
- **Signs and symptoms**
 - Tumours present as a slow-growing, mobile or fixed mass of various durations.
 - Usually asymptomatic but pain or tenderness may be seen in few cases.
 - Facial nerve paralysis and facial muscle weakness may be evident.

Histopathology

- Usually, tumour is surrounded by thin capsule and composed of cells of varying degree of differentiation.
 - Well-differentiated cells resemble normal acinar cells.
 - Less-differentiated cells resemble embryonic ducts and immature acinar cells.
- The individual cell characteristics can be categorized as *acinar, intercalated duct-like, vacuolated, clear and nonspecific glandular cells.*
 - *Acinar cells:* These cells are of large size, round to polygonal in shape with eccentric nucleus and granular basophilic cytoplasm.
 - *Intercalated duct-like cells:* These cells are smaller than acinar cells, and cuboidal in shape with eosinophilic cytoplasm and centrally placed nuclei.
 - *Vacuolated cells:* These are unique and peculiar cells. The cells are typically about the size of well-differentiated acinar cells. These have eccentric nuclei that are less chromatic and more pleomorphic. Cytoplasm shows several vacuoles or a single large vacuole.
 - *Nonspecific glandular cells:* The most difficult to describe and are defined by the absence of features that are characteristic of other four cell types. These usually form a syncytium of cells with indistinct cell boundaries and eosinophilic cytoplasm. The nuclei are typically larger and more vesicular and pleomorphic than those of other types. Mitotic figures are more evident.
- It exhibits four growth patterns:
 1. *Solid growth pattern:* Classic pattern
 - It consists of numerous well-differentiated acinar cells arranged in pattern that resembles normal parenchyma. The absence of

striated ducts should distinguish it from normal parenchyma.
- It is composed of sheets of tumour cells that frequently have an organoid configuration.
- The tumour cells are separated and surrounded by thin fibrous septa that contain small invisible capillaries.

2. *Microcystic pattern:* More common pattern
- It has numerous small cystic spaces.
- Acinar cells are dominant cell type; however, vacuolated and intercalated duct-like cells can also be prominent.
- Microcystic spaces may result from coalescence of intracellular vacuoles of ruptured cells. Proteinaceous or mucinous material may pool in microcystic spaces.

3. Papillary cystic growth pattern
- It is characteristic of one or more cystic structures that contain proliferations of epithelium.
- Usually, cysts may be small with a few folds of lining epithelia projecting into the lumina. Sometimes cystic structures can be large with long stalks, fronds or masses of glandular epithelium within the lumina.
- Intercalated duct-like and nonspecific glandular cells are predominantly seen.
- Some of the epithelial projections have thin fibrovascular cores, whereas others appear to be masses of epithelium without supporting stroma.

4. *Follicular pattern:* Least frequently encountered
- This pattern has a definite thyroid-like appearance.
- Variable sized, ovoid to round cystic spaces are lined by cuboidal to low columnar epithelial cells.
- Many of the cystic spaces contain an eosinophilic proteinaceous material.

Differential diagnosis

- Normal parotid gland
- Cystadenocarcinoma
- Clear cell carcinoma

Prognosis and predictive factors

- Total surgical excision of gland is advised.

- Poor prognosis, when it is associated clinically with pain, fixation and histopathologically with atypia and increased mitosis.

Carcinoma ex pleomorphic adenoma

(Synonym: Carcinoma ex benign mixed tumour)
It is a malignant transformation of a pre-existing pleomorphic adenoma.

Pathogenesis

- Carcinoma ex pleomorphic adenoma is malignant transformation of a pre-existing pleomorphic adenoma.
- The different phases of carcinoma ex pleomorphic adenoma include:
 - In the earliest phase, carcinoma cells with large atypical nuclei replace the neoplastic ductal luminal cells while retaining an intact layer of non-atypical myoepithelial cells of the pre-existing pleomorphic adenoma. This can be considered a form of *carcinoma in situ* and there is no metastatic potential.
 - With time, carcinoma cells may break out from the confines of the neoplastic myoepithelial sheath and invade into the surrounding stroma. The prognosis is excellent with complete excision.
 - If the invasion extends beyond the fibrous capsule of the parent pleomorphic adenoma, the carcinoma ex pleomorphic adenoma is considered *invasive*.

Clinical features

- **Age.** 60–70 years.
- **Gender.** Female predilection.
- **Location.** Parotid gland, submandibular gland, minor salivary gland of palate.
- **Signs and symptoms**
 - Long-standing pleomorphic adenoma of more than 3 months, showing rapid growth, is reported.
 - Patient may complain of painless mass; but pain, facial nerve palsy and skin fixation may also occur.

Histopathology

- The malignant component is most commonly poorly differentiated adenocarcinoma (salivary duct type or not otherwise specified) or undifferentiated carcinoma.

- Histopathologic documentation of a previous pleomorphic adenoma or areas of pleomorphic adenoma are evident within malignant tumour, a diagnosis of carcinoma ex pleomorphic adenoma is given.
- Infiltrative, destructive growth pattern is the most reliable diagnostic criterion.
- Minimal cellular atypia is seen.
- Malignant cells exhibit nuclear hyperchromasia and pleomorphism.

Differential diagnosis

- Carcinoma ex-Warthin's tumour
- Adenocarcinoma
- Oncocytic carcinoma

Prognosis and predictive factors

- Wide local surgical excision with contiguous lymph node dissection is done.
- If invasion is more, adjuvant radiation therapy is recommended.

Adenocarcinoma—NOS

(*Synonym: Unclassified adenocarcinom*a)

- It is a tumour that exhibits ductal differentiation but lacks histopathological features similar to any classifiable salivary gland tumour.
- The term *not otherwise specified* meaning that we cannot categorize a tumour as one of the specific types listed in the classification.

Clinical features

- **Age.** 40–80 years.
- **Gender.** Male predilection.
- **Location.** Parotid salivary gland.
- **Signs and symptoms**
 - Usually, it manifests as asymptomatic solitary swelling.
 - Few patients may complain of pain and nerve involvement.

Histopathology

- Glandular or ductal structures with an infiltrative growth are features of this tumour.
- The tumour is graded histopathologically into low, intermediate and high

grades depending on the ductal differentiation.

- Tumour cells are cuboidal to ovoid in shape, nuclear pleomorphism or hyperchromasia and rare mitosis is evident in these cells.
- High-grade tumours exhibit more features of anaplasia, increase in mitotic figure, cellular and nuclear pleomorphism.
- In few areas, cords and nests of cells are also seen.

Prognosis and predictive factors

- Treatment and prognosis depends on grade of the tumour.
- The higher the grade more extensive surgery is needed and poorer the prognosis.

Incidence of malignant tumours of salivary gland in decreasing order

Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Adenocarcinoma
Acinic cell carcinoma
Polymorphous low-grade adenocarcinoma (PLGA)

Tumour-like lesions

Necrotizing sialometaplasia

- It is a benign, necrotizing, self-healing, inflammatory condition of the salivary glands.
- It is a tumour-like lesion, which mimics a malignant salivary gland tumour clinically and histopathologically.

Pathogenesis

There is ischaemic injury to salivary gland followed by regeneration.

Clinical features

- **Age.** 17–80 years.
- **Gender.** Male predilection.
- **Location.** Minor salivary glands of palate, retromolar and buccal mucosa.
- **Signs and symptoms**
 - Palatal lesions present commonly as deep, crater-like ulcers. The ulcers are usually unilateral but sometimes so are the bilateral lesions.
 - This condition may also appear as submucosal nodular swellings that may slough and leave characteristic crater-like ulcers.
 - Typically, the lesions are asymptomatic; however, patients complain of numbness and pain or burning sensation.
 - The time required for complete healing depends on the size of the lesion, but in most cases, it varies from 3 to 12 weeks.

Radiographic features

Erosion of underlying bone is evident.

Histopathology

- The two key features are:
 - Squamous metaplasia of ductoacinar units.
 - Lobular necrosis with preservation of the lobular architecture of glandular tissue.
- *Squamous metaplasia*
 - The metaplastic squamous nests are bland appearing vary moderately in size and shape and are arranged in a lobular pattern.

- These nests are set in a background of granulation tissue and diffuse inflammation.
- The majority of metaplastic nests are composed of squamous cell with abundant pink cytoplasm and uniform bland nuclei. Sometimes, basaloid cells with hyperchromatic nuclei are predominantly seen.

- *Lobular necrosis*
 - Completely or partially necrotic lobules are intermixed with metaplastic lobules.
 - The necrotic lobules are composed of small, acinus-sized pools of mucin that are surrounded by thin, necrotic septa.
 - The mucin pools may coalesce and extend into adjacent tissue.
 - Granulation tissue may be prominent at the periphery of necrotic areas.

Differential diagnosis

- Squamous cell carcinoma
- Mucoepidermoid carcinoma
- Adenocarcinoma

Prognosis and predictive factors

It is a self-healing lesion, hence no treatment is necessary.

Sjögren's syndrome

(Synonym: Sicca syndrome)

- It is a chronic, systemic autoimmune disorder which involves salivary glands and lacrimal glands resulting in dryness in mouth and eyes—xerostomia (dry mouth) and xerophthalmia (dry eyes), respectively.
- Keratoconjuctivitis sicca: Dryness of both cornea and conjunctiva.
- Sicca complex includes both xerostomia and xerophthalmia.

Types

- Primary Sjögren's syndrome: It is associated with only sicca complex, but not with any autoimmune disorders.
- Secondary Sjögren's syndrome: It includes sicca complex with autoimmune disorders.

Pathogenesis

- **Genetic changes**
 - Primary type: It is associated with both *HLA-B8* and *HLA-DR3* alterations.
 - Both types are associated with HLA-DRw52 changes.
- **Hormonal changes**
 - Infections
 - Immunologic change is the main intrinsic factor responsible for this disease.
 - Cytomegalovirus, paramyxovirus and Epstein–Barr virus may have a role in the pathogenesis of this condition.

Clinical features

- **Age.** 40–50 years.
- **Gender.** Female predilection.
- **Location.** Parotid salivary gland, sometimes submandibular gland and minor salivary glands.
- **Signs and symptoms**

1. ***Primary Sjögren's syndrome***

- *Ocular dryness:* Symptoms of dry eyes—keratoconjunctivitis sicca.
 - Reduced tear production by lacrimal glands.
 - Lacrimal inflammation causes decreased aqueous layer of tear film; however, mucin production is normal and may result in mucoid discharge.
 - Patient complains of scratchy, gritty sensation or perceived presence of foreign body in eye.
 - Defects of ocular surface epithelium develop and can be demonstrated with *rose bengal dye.*
 - Vision may become blurred and sometimes aching pain is present.
 - Ocular manifestations are least severe in morning on wakening and become more pronounced as day progresses.
 - *Schirmer test:* To confirm decreased tear secretion—A standardized strip of sterile filter paper is placed over the margin of the lower eyelid between the medial two-thirds and lateral third of lid of unanaesthetized eye, so that the tabbed end rests just inside the lower lid.

By measuring the length of wetting of filter paper, tear production can be assessed.

Values less than 5 mm (after a 5-minute period) are considered diagnostic

of keratoconjunctivitis.

- *Oral:*
 - Decreased salivary secretions; severity of dryness can vary widely from patient to patient.
 - Saliva may appear frothy, with a lack of usual pooling saliva in the floor of mouth.
 - Affected patient may complain of difficulty in swallowing altered taste or difficulty in wearing dentures.
 - The tongue often becomes fissured and exhibits atrophy of the papillae.
 - The oral mucosa may be red and tender, usually as a result of secondary candidiasis.
 - Denture sore mouth and angular cheilitis are common.
 - Increased frequency of dental caries is seen due to lack of salivary secretion.
- *Salivary gland:* Major salivary glands are diffuse, firm and enlarged in size.
 - This swelling is usually bilateral, non-tender and may be intermittent or persistent in nature.
 - Reduced salivary flow will increase the risk of retrograde bacterial sialadenitis.
- *Others:* Lymphadenopathy, primary biliary cirrhosis, Raynaud's phenomenon, interstitial nephritis, interstitial lung fibrosis, vasculitis and peripheral neuropathies.

2. ***Secondary Sjögren's syndrome:*** It includes characteristic signs and symptoms of primary Sjögren's syndrome and clinical features of autoimmunity disorders like systemic lupus erythematosus, polyarteritis nodosa, polymyositis, scleroderma or rheumatoid arthritis.

- **Sialography**
 - It often reveals punctate sialectasia.
 - Lack of normal ductal system, typically demonstrating a *fruit laden tree pattern, branchless tree pattern* or *cherry blossom effect*.
- **Scintigraphy** with radioactive technetium-99m pertechnetate characteristically shows decreased uptake and delayed emptying of the isotope.
- **Laboratory findings**
 - ESR is high.
 - Elevated serum immunoglobulin (Ig) levels, especially IgG.
 - Positive rheumatoid factor.
 - Anti-nuclear antibodies (ANA): Anti-SS-A and anti-SS-B.

- Salivary duct autoantibodies can be demonstrated in secondary Sjögren's syndrome.

Histopathology

- Basic microscopic finding in Sjögren's syndrome is a lymphocytic infiltration of salivary gland with destruction of acinar units, although the lobular architecture is preserved.
- Proliferation of ductal epithelium and myoepithelium to form *epimyoepithelial islands.*
 (Both these histological changes are identical to the Mikulicz's disease.)
- Atrophy of glands sequential to lymphocytic infiltration is seen.
- Biopsy of minor salivary glands of the lower lip has become a useful test in the diagnosis of Sjögren's syndrome—a 1.5–2 cm incision is made on clinically normal lower labial mucosa, parallel to vermilion border and lateral to the midline, allowing the harvest of five or more accessory glands. These glands are examined hispathologically for the presence of focal chronic inflammatory aggregates (50 or more lymphocytes and plasma cells). The finding of more than one focus of 50 or more cells within a 4 mm^2 area of glandular tissue is supportive of diagnosis of Sjögren's syndrome. The greater is the number of foci, the greater is the correlation with this diagnosis. However, it is not a 100% reliable test in the diagnosis of Sjögren's syndrome:
 - Some patients diagnosed with Sjögren's syndrome will show no significant labial gland inflammation; conversely, examination of labial glands removed from non-Sjögren's syndrome patients incidentally show focal lymphocytic infiltrates sometimes.
 - Sjögren's syndrome patients who smoke have been shown to have low frequency of abnormal lymphocytic foci scores in labial gland specimens.
- Few authors advocate incisional biopsy of parotid gland through a posterior auricular approach instead of labial salivary gland biopsy. It is a more sensitive technique in demonstrating inflammatory changes that support the diagnosis of Sjögren's syndrome. But, some authors think that this technique confers no increased benefit over labial gland biopsy and parotid biopsy may enable to develop lymphoma and sialadenosis or sarcoidosis.

Diagnostic criteria for Sjögren's syndrome (San Diego criteria)

- **Primary Sjögren's syndrome**
 - *Keratoconjunctivitis sicca*
 - It is characterized by corneal and conjunctival epithelial staining with rose bengal stain observed through slit lamp.
 - Reduced tear meniscus and break-up time.
 - Schirmer's test ≤5 mm/5 minutes.
 - *Focal sialadenitis* in labial salivary gland biopsy specimen with focus score >1 focus/4 mm2.
- **Secondary Sjögren's syndrome**
 - Rheumatoid arthritis or other connective tissue diseases.
 - Either one or both of the criteria for primary Sjögren's syndrome.

Prognosis and predictive factors

- The treatment of Sjögren's syndrome is mostly supportive.
- The dry eyes are best managed by periodic use of artificial tears containing methylcellulose.
- Artificial saliva is available for the treatment of xerostomia. Symptoms can be relieved by the use of oral hygiene products that contain lactoperoxidase, lysosome and lactoferrin. Sialogogue medication such as pilocarpine and cevimeline can be useful to stimulate salivary flow, if enough functional salivary tissue still remains.
- Patients with Sjögren's syndrome have an increased risk for lymphoma (predominantly non-Hodgkin's B-cell lymphoma).

Benign lymphoepithelial lesion or Mikulicz's disease

(Synonyms: Mikulicz's disease; myoepithelial sialadenitis; dacryosialoadenopathia)

- In 1988, Johann von Mikulicz, a German surgeon, first reported a case of chronic bilateral lacrimal gland enlargement associated with the enlargement of salivary glands.
- It is a chronic condition characterized by the abnormal enlargement of the salivary and lacrimal glands. The tonsils and other glands in soft tissue of face and neck may also get affected.
- *Mikulicz's disease:* It includes involvement of salivary and lacrimal glands.
- *Mikulicz syndrome:* It includes involvement of salivary and lacrimal glands along with other systemic diseases.

Pathogenesis

- Exact cause is unknown, although may be due to immune system dysregulation.
- It may be due to secondary to other diseases like tuberculosis, sarcoidosis or lymphomas.

Clinical features

- **Age.** 40–50 years.
- **Gender.** Female predilection.
- **Location.** Parotid salivary gland, sometimes, submandibular salivary gland and minor salivary glands.
- **Signs and symptoms**
 - Most of the cases develop as a component of Sjögren's syndrome. Few lesions are not associated with Sjögren's syndrome and are usually unilateral in occurrence.
 - Salivary gland involvement
 - Sudden onset of xerostomia causes difficulty in swallowing and increased incidence of tooth decay.
 - Asymptomatic or mild pain will be present.
 - It appears as a firm, diffuse swelling of the salivary gland.
 - Lacrimal gland involvement
 - Painless enlarged lacrimal glands are seen.
 - Decreased or no tear is present.
 - Uveitis.
 - Sometimes, recurrent fever may be accompanied by above symptoms.

Histopathology

- It shows heavy lymphocytic infiltrate associated with destruction of salivary acini, which may or may not show germinal centres.
- The ductal cells and surrounding myoepithelial cells become hyperplastic forming a characteristic group of cells, *epimyoepithelial islands,* throughout the lymphoid proliferation.
- A characteristic change also found in advanced lesions like deposition of eosinophilic, hyaline material in epithelial islands.

Note: Epimyoepithelial islands also can be found in low-grade salivary

gland lymphomas and mucosa-associated lymphoid tissue lymphomas (MALT lymphomas, marginal zone B-cell lymphomas).

Prognosis and predictive factors

- The surgical excision of the involved gland is required.
- The prognosis in most cases is good.
- The management (symptomatic) of patients is similar to Sjögren's syndrome patients.
- Individuals having Mikulicz's disease are at high risk of developing lymphomas.

Other lesions

Sialolithiasis

(Synonyms: Salivary duct calculi; salivary duct stone)
Sialoliths are calcified structures that develop within the salivary ductal system or salivary gland.

Pathogenesis

- It arises from deposition of calcium salts around a nidus of debris within the duct lumen.
- The debris includes altered salivary mucins, desquamated epithelial cells, bacteria, foreign bodies or products of bacterial decomposition.
- The cause of sialolith is unclear, but its formation can be promoted by chronic sialadenitis and partial obstruction.
- Sialolith development is not related to any systemic derangement in calcium and phosphorus metabolism.

Clinical features

- **Age.** 20–40 years.
- **Sex.** No sex predilection.
- **Location.** Submandibular gland duct (because Warthin's duct is long, tortuous in upward path (against gravity) and thicker, mucoid secretions), rarely, parotid salivary gland and minor salivary gland.
- **Signs and symptoms**
 - It causes episodic pain or swelling of the affected gland, especially at meal time or thought of meal.
 - Severity of symptoms varies depending on degree of obstruction and amount of resultant back pressure produced within gland.
 - If the stone is located towards the terminal portion of duct, then a hard mass may be palpated beneath the mucosa.
 - Minor salivary glands sialolith is asymptomatic but may produce local swelling or tenderness of the affected gland.

Radiographic features

- Sialoliths appear as radiopaque mass. However, not all stones are visible on standard radiographs because of the degree of calcification of some

lesions.
- These may be discovered anywhere along the length of duct or within the gland itself.
- Sialoliths in terminal portion of the submandibular duct are best demonstrated with an occlusal radiograph.

Histopathology

- **Gross examination**
 - Sialoliths appear as round, oval or cylindrical and yellow or yellowish brown hard mass.
 - Sialoliths are usually solitary, but occasionally two or more may be occurred.
- **Microscopic features**
 - The calcified mass exhibits concentric laminations that may surround a nidus of amorphous debris.
 - The associated duct epithelium shows squamous, oncocytic or mucous cell metaplasia.
 - Periductal inflammation is also evident.
 - The ductal obstruction is usually associated with an acute or chronic sialadenitis of the feeding gland.
- **Chemical composition of calculi**
 - Calcium phosphate(75%)
 - Calcium carbonate (20%)
 - Soluble salts, organic material and water (5–6%)

Prognosis and predictive factors

- Gentle massage.
- Moist heat and increased fluid intake.
- Large sialoliths should be surgically excised.
- Salivary gland endoscopy can be advised.

Sialadenitis

- Sialadenitis is an inflammation of salivary gland, which mainly involve acino-parenchyma of the gland.
- It may be acute or chronic form. Usually, acute form more often affects the major salivary glands than the minor glands.

Pathogenesis

- **Infectious causes**
 - Viral infections are commonly involved, which include mumps—paramyxo, coxsackie A, choriomeningitis, parainfluenza and cytomegalo viruses.
 - Most of the bacterial infections arise as a result of ductal obstruction or decreased salivary flow, allowing retrograde spread of bacteria throughout the ductal system.
 - Blockage of duct can be caused due to sialolithiasis, congenital strictures or compression by an adjacent tumour.
 - Decreased salivary flow may also be due to dehydration, debilitation, medication, recent surgery or acute parotitis.
- **Noninfectious causes:** Sjögren's syndrome, sarcoidosis, radiation therapy, malnutrition, renal failure and various allergens.

Clinical features

- **Age.** 20–40 years.
- **Sex.** No sex predilection.
- **Location.** Parotid salivary gland, submandibular salivary gland and minor salivary glands.
- **Signs and symptoms**
 - *Acute bacterial sialadenitis*
 - The affected gland will be swollen and painful.
 - The overlying skin may be warm and erythematous.
 - An associated low-grade fever and trismus may be present.
 - A purulent discharge is observed from the duct orifice when the gland is massaged.
 - *Chronic bacterial sialadenitis*
 - It is commonly caused by recurrent or persistent ductal obstruction of Warthin's duct. Periodic swelling and pain occur within the affected gland, usually developing at mealtime when salivary flow is stimulated
 - Sialography: Sialectasia (ductal dilatation) proximal to area of obstruction is seen.
 - Chronic parotitis: Stensen's duct may show a characteristic sialographic pattern, *sausaging*, which reflects a combination of dilatation plus ductal strictures from scar formation.
 - Chronic sialadenitis can occur in minor salivary glands also, as a

result of blockage of ductal flow or local trauma.

Histopathology

- *Acute sialadenitis:* Accumulation of neutrophils within ductal system and acini is seen.
- *Chronic sialadenitis:* Scattered or patchy infiltration of the salivary parenchyma by lymphocytes and plasma cells is seen. Atrophy of acini is common along with ductal dilatation. If associated fibrosis is present, chronic sclerosing sialadenitis.

Prognosis and predictive factors

- Treat the causative medical condition.
- Warm compresses, sialogogues (lemon drops) is given.
- External salivary gland massage is advised, if tolerated.
- Antibiotics can be advised.

Sialorrhoea

(Synonym: Ptyalism)
Sialorrhoea means *excess salivation*.

- *Minor sialorrhoea:* Local irritations such as aphthous ulcers or ill-fitting dentures.
- *Episodic sialorrhoea:* It may occur as a protective buffering system to neutralize stomach acid in individuals with gastroesophageal reflex disease.
- *Major sialorrhoea:* Patients with new dentures, rabies, heavy metal poisoning and antipsychotic agents.
- *Drooling of saliva:* Mentally retarded patients, individuals with resected mandible, neurologic disorders and individuals with poor neuromuscular control.

Clinical features

- Excess salivation, especially among mentally retarded children can cause erosion or ulcers around oral cavity, chin and neck that can become secondarily infected.
- Drooling and choking of saliva is common.
- Idiopathic paroxysmal sialorrhoea: Individuals experience short episodes

of excessive salivation lasting from 2 to 5 minutes. These episodes are associated with a prodrome of nausea or epigastric pain.

Prognosis and predictive factors

- Anticholinergic medication is advised.
- Surgical relocation of ducts into posterior part of oral cavity is done for people with poor neuromuscular control.

Xerostomia

Xerostomia is sensation of dryness of mouth, caused by numerous causes other than the salivary gland changes. It is not a disease, but it can be a symptom of certain diseases.

Pathogenesis

- **Temporary causes**
 - Psychological
 - Anxiety and depression
 - Drugs used for psychological problem
 - Duct calculi
 - Sialadenitis
 - Drugs
 - *Antihistamine agents:* Diphenhydramine, chlorpheniramine
 - *Antidepressant agents:* Amitriptyline, citalopram, fluoxetine, paroxetine
 - *Antipsychotic agents:* Phenothiazine derivatives, haloperidol
 - *Sedatives and anxiolytic agents:* Diazepam, lorazepam, alprazolam
 - *Antihypertensive agents:* Reserpine, methyldopa, chlorothiazide, calcium channel blockers
 - *Anticholinergic agents:* Atropine, scopolamine
- **Permanent causes**
 - Salivary gland aplasia
 - Sjögren's syndrome
 - Systemic disorders like diabetes mellitus, Parkinson's disease, cystic fibrosis, sarcoidosis, vitamin deficiency
 - Radiotherapy
 - Surgical desalivation

Clinical features

- **Age.** >40 years.
- **Signs and symptoms**
 - It is important to establish:
 - Whether the dryness is continual or intermittent?
 - Whether it is accompanied by pain or swelling or both?
 - Whether swelling is unilateral or bilateral?
 - Whether there is any relevant history of anxiety, stress or depression, systemic disorder, irradiation, trauma, surgery or medication?
 - Unilateral dryness with pain and swelling in affected gland on stimulation—duct calculus.
 - Sjögren's syndrome: It produces bilateral swelling, often constant and accompanied by other symptoms.
 - Mild xerostomia: Patient complains of dry or burning sensation but mucosa appears normal.
 - Severe xerostomia: Mucosa appears dry and atrophic, sometimes inflamed or often pale and translucent. Tongue shows atrophy of papillae, inflammation, fissuring and cracking. Patient complains of soreness; burning and pain of mucous membrane and tongue are seen.
 - Increased prevalence of oral candidiasis is seen because of reduction in the cleansing and antimicrobial activity.
 - Chronic xerostomia predisposes to rampant dental caries and subsequent loss of teeth.
 - Xerostomia associated with radiation therapy—radiation-induced caries.
 - Patient may complain of difficulty in swallowing and mastication.

Prognosis and predictive factors

- Artificial salivary substitutes are advised and continuous sips of water throughout the day make the patient more comfortable.
- If the dryness is secondary to the patient's medication, then discontinuation or dose modification in consultation with the patient's physician may be considered.
- Systemic pilocarpine is a parasympathetic agonist that can be used as a sialogogue.
- Since patients with xerostomia are more prone to dental caries, frequent dental visits are recommended.

Key points

- *Pleomorphic adenoma* is the most common benign salivary gland neoplasm consisting of cells exhibiting ability to differentiate into epithelial (ductal and nonductal—myoepithelial) and mesenchymal cells (chondroid, myxoid and osseous structures).
- *Warthin tumour* is characterized by proliferation of both luminal and non-luminal cells.
- Oncocytes are large cells with prominent eosinophilic granular cytoplasm with a centrally placed nuclei.
- *Basal cell adenoma* is composed of basaloid cells arranged in solid, trabecular, tubular or membranous patterns.
- *Canalicular adenoma* is composed of columnar epithelial cells arranged in a single or double layers forming branching cords in a loose connective tissue stroma.
- *Mucoepidermoid carcinoma* is a malignant salivary gland tumour, which is composed of three cell types, mucous cells, intermediate cells and epidermoid cells.
- *Adenoid cystic carcinoma* consists of islands of basaloid cells containing multiple cylindrical, cyst-like spaces resembling *Swiss cheese* or *honeycomb pattern.*
- *Polymorphous low-grade adenocarcinoma* shows infiltration of peripheral cells into adjacent tissue in a single file fashion or Indian file fashion.
- *Acinic cell carcinoma* is a malignant salivary gland neoplasm in which the neoplastic cells express acinar differentiation.
- *Adenocarcinoma—not otherwise specified* exhibits ductal differentiation but lacks histopathological features similar to any classifiable salivary gland tumour.
- *Necrotizing sialometaplasia* is a benign, necrotizing, self-healing, inflammatory condition of the salivary glands.
- *Sjögren syndrome* is a chronic, systemic autoimmune disorder which involves salivary glands and lacrimal glands resulting in xerostomia and xerophthalmia.
- *Sialadenosis* is an unusual nonneoplastic, noninflammatory enlargement of salivary glands.
- *Sialoliths* are calcified structures that develop within the salivary ductal system or salivary gland.
- *Sialorrhoea* means *excess salivation.*
- *Xerostomia* is sensation of dryness of mouth, caused by numerous causes

other than the salivary gland changes.

Frequently asked questions

1. Discuss the pathogenesis, clinical features and histopathology of pleomorphic adenoma.
2. Warthin's tumour.
3. Oncocytoma.
4. Canalicular adenoma.
5. Ductal papillomas.
6. Discuss the pathogenesis, clinical features and histopathology of mucoepidermoid carcinoma.
7. Adenoid cystic carcinoma.
8. Polymorphous low-grade carcinoma.
9. Carcinoma ex pleomorphic adenoma.
10. Sjögren's syndrome.
11. Mikulicz's disease.
12. Sialolithiasis.
13. Xerostomia.

CHAPTER 4

Odontogenic tumours

Remnants of odontogenic epithelium and their role in the pathogenesis of odontogenic tumours

Tooth development can be divided into three overlapping phases—initiation, morphogenesis and histogenesis. During initiation, the sites of the future teeth are established with the appearance of tooth germs along an invagination of the oral epithelium called the dental lamina. During morphogenesis, the shape of the tooth is determined by a combination of cell proliferation and cell movement. During histogenesis, differentiation of cells (begun during morphogenesis) proceeds to give rise to the fully formed dental tissues.

Dental lamina and vestibular lamina

- At the 6th week of intrauterine life, the oral epithelium thickens and invaginates into the mesenchyme to form the primary epithelial band.
- By 7th week, the primary epithelial band divides into two processes—a buccally located *vestibular lamina* and lingually situated *dental lamina* (Fig. 4.1).
- The dental lamina contributes to the development of the deciduous teeth.
- The vestibular lamina contributes to the development of vestibule in the mouth.

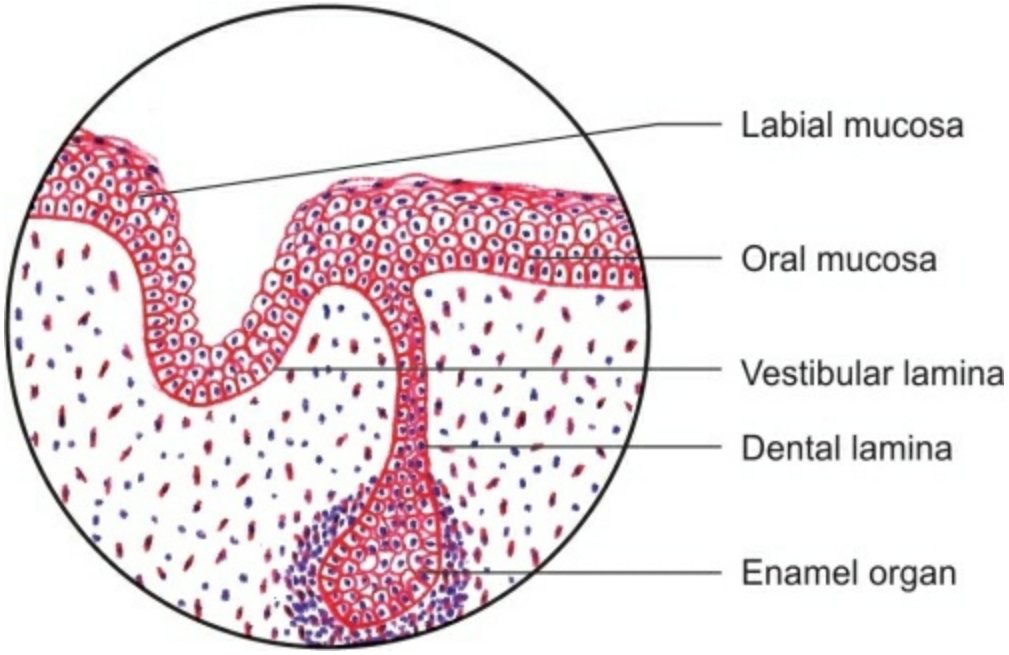


FIG. 4.1 Enamel organ forming at the end of the dental lamina and cavitation of vestibular lamina leading to the formation of a vestibule.

Successional lamina

- It develops from the lingual (or palatal) portion of the dental lamina.
- It is destined to provide the anlage for the permanent teeth replacing the primary predecessors—incisors for incisors, canines for canines and premolars for primary molars (Fig. 4.2).

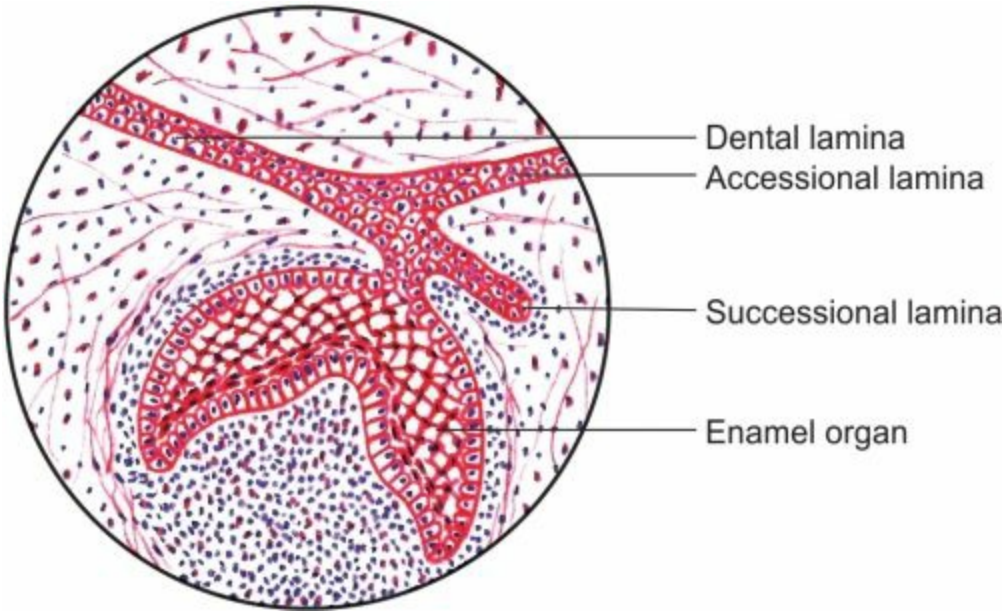


FIG. 4.2 Formation of deciduous tooth germ on the labial aspect of dental lamina and free end of dental lamina proliferates into the ectomesenchyme as a successional lamina and accessional lamina, providing the anlage for a permanent tooth replacing the primary tooth and permanent molars, respectively.

Accessional lamina

- At the 4th fetal month, a distal extension of the dental lamina grows backwards underneath the oral epithelium and provides the anlage for permanent molars known as the *accessional lamina* (Fig. 4.2).
- The earliest sign of the enamel organ of the first permanent molar is seen in the 4th intrauterine month. The second permanent molar appears shortly before the birth and the third molar is initiated when the child is about 4–5 years of age.

Disintegration of the dental laminae complex

- Soon after the establishment of the tooth germs, the dental laminae begin to fragment or disintegrate due to ectomesenchymal invasion and/or programmed cell death. But, some cells of the dental lamina persist and tend to aggregate through proliferation into nests known as *cell rests of Serre (Serre pearls or glands of Serre)*.
- The successional laminae and the accessional laminae also disintegrate and give rise to epithelial cell remnants.

Rests of malassez

- Hertwig's epithelial root sheath (HERS), a double layer of epithelial cells (inner and outer dental epithelium) determines the shape of the root and helps to form the root cementum.
- The fragmentation of the HERS results in the creation of a network of epithelial cells around the root.
- Finally after programmed cell death, only scattered surviving remnants of isolated epithelial cells or cell clusters will form *epithelial cell rests of Malassez.*

The majority of epithelial residues persist throughout life in the gubernacular canals and periodontal membranes as vital, inactive (resting), single cells or cell clusters. Some of the cell rests seem to be triggered to proliferation by unknown stimulus resulting in production of well-recognized pathological entities (e.g. odontogenic tumours and cysts) later in life.

Classification of odontogenictumours of the jaws (WHO, 2005)

Benign

- Odontogenic epithelium with mature fibrous stroma without odontogenic ectomesenchyme
 1. Ameloblastoma
 2. Adenomatoid odontogenic tumour
 3. Squamous odontogenic tumour
 4. Calcifying epithelial odontogenic tumour
 5. Keratocystic odontogenic tumour
- Odontogenic epithelium with odontogenic ectomesenchyme with or without hard tissue formation
 1. Ameloblastic fibroma
 2. Ameloblastic fibrodentinoma
 3. Ameloblastic fibro-odontoma
 4. Complex odontoma
 5. Compound odontoma
 6. Odontoameloblastoma
 7. Calcifying cystic odontogenic tumour
- Odontogenic ectomesenchyme with or without odontogenic epithelium
 1. Odontogenic fibroma

2. Odontogenic myxoma
3. Cementoblastoma

Malignant

- Odontogenic carcinoma
 1. Malignant ameloblastoma
 2. Ameloblastic carcinoma
 3. Ghost cell odontogenic carcinoma
 4. Clear cell odontogenic carcinoma
 5. Primary intraosseous squamous cell carcinoma
- Odontogenic sarcoma
 1. Ameloblastic fibrosarcoma
 2. Ameloblastic fibrodentino- and fibro-odontosarcoma

Molecular pathogenesis of odontogenic tumours

The development and progression of odontogenic tumours are affected by alterations of many genes and molecules. In particular, the characteristics of odontogenic tumours appear to depend on the molecular mechanisms associated with: (i) tooth development, (ii) bone metabolism and (iii) the malignant potential of tumours. Although, the exact aetiology and pathogenesis of odontogenic tumours remain unknown recent studies have identified various molecular alterations responsible for tumour development and progression (Table 4.1).

Table 4.1

Various molecular alterations responsible for tumour development and progression

Molecules associated with tumourigenesis and/or tumour cell differentiation	
• Oncogenes	Ras, Myc, Fos
• Tumour-suppressor genes	p53, APC
• Oncoviruses	HPV, EBV
• Growth factors	TGF-α, TGF-β, FGF-1, FGF-2, HGF
• Telomerase	Telomerase
• Cell-cycle regulators	Cyclin D1, $p16^{INK4a}$, $p21^{WAF1/Cip1}$, $p27^{Kip1}$
• Apoptosis-related factors	Bcl-2 family, IAP family, Fas, TNF-α, p53
• Regulators of tooth development	SHH pathway, Wnt pathway
• Hard tissue-related proteins	Enamel proteins, BSP, osteonectin, osteocalcin, osteopontin, BMP
Molecules associated with tumour progression	
• Cell-adhesion molecules	E-selectin, ICAM-1, VCAM-1, E-cadherin, integrins, CD44
• Matrix-degrading proteinases	MMP-1, MMP-2, MMP-9, TIMP-1, TIMP-2, Heparanase
• Angiogenic factors	VEGF
• Osteolytic cytokines	IL-1, IL-6, TNF-α, PTHrP, RANKL/OPG

HPV, Human papilloma virus; **EBV**, Epstein–Barr virus; **TGF**, Transforming growth factor; **FGF**, Fibroblast growth factor; **HGF**, Hepatocyte growth factor; **IAP**, Inhibitor of apoptosis protein; **TNF**, Tumour necrosis factor; **SHH**, Sonic hedgehog; **BSP**, Bone sialoprotein; **BMP**, Bone morphogenetic protein; **ICAM**, Intercellular adhesion molecule; **VCAM**, Vascular cell adhesion molecule; **MMP**, Matrix metalloproteinase; **TIMP**, Tissue inhibitor of metalloproteinases; **VEGF**, Vascular endothelial growth factor; **IL**, Interleukin; **PTHrP**, Parathyroid hormone-related protein; **RANKL**, Receptor activator of nuclear factor-κB ligand; **OPG,** Osteoprotegerin.

Ameloblastoma

(Synonyms: Adamantinoma; adamantoblastoma)

- The ameloblastoma is a true neoplasm of enamel organ-type tissue which does not undergo differentiation to the point of enamel formation.
- Robinson defined ameloblastoma as "usually unicentric, non-functional, intermittent in growth, anatomically benign and clinically persistent".
- Based on clinical, radiographic and histopathological characteristics, the following variants of ameloblastoma can be presently distinguished:
 - Classic solid/multicystic ameloblastoma (SMA)
 - Unicystic ameloblastoma (UA)
 - Peripheral ameloblastoma (PA)
 - Desmoplastic ameloblastoma (DA)

Note: Recently, desmoplastic ameloblastoma is added as a new subtype rather than a histologic variant due to following reasons:

- Difference in anatomic location compared to other forms of ameloblastoma
- Unusual radiographic appearance
- Atypical morphology of epithelial component
- Marked stromal desmoplasia

Solid/multicystic ameloblastoma

(Synonym: Conventional ameloblastoma)

The term *ameloblastoma* was coined by Churchill in 1934. It is the second most common odontogenic neoplasm (first being odontoma).

Definition

The solid/multicystic ameloblastoma (SMA) is a slow growing, locally invasive, epithelial odontogenic tumour of the jaws with a high rate of recurrence, if not removed adequately, but with virtually no tendency to metastasize *(WHO, 2005)*.

Pathogenesis

Tumour can arise from any of the following:

- Cell rests of enamel organ.
- Disturbances in developing enamel organ.
- Epithelium of odontogenic cysts—dentigerous cysts or odontomas.
- Heterotrophic epithelium in other parts of body especially in pituitary gland (Rathke's pouch ameloblastoma).

Clinical features

- **Age.** 30–40 years.
- **Gender.** Male predilection.
- **Location.** Posterior region of the mandible.
- **Signs and symptoms**
 - It is a slow growing, but locally invasive tumour with a high rate of recurrence, if not removed adequately.
 - Initially, few or no clinical signs are seen.

- In later stages, there will be a gradual increase in swelling leading to facial deformity.
- Continued enlargement of tumour may cause surrounding bone to become so thin that crepitation or egg-shell crackling may be elicited.
- Teeth in the lesional area may become mobile and pathological fracture of jaws may occur sometimes.
- Pain may be present only in some cases. It may be either due to pressure of the tumour on peripheral nerves or secondary infection.

Radiographic features

- *Unilocular type:* Well-defined radiolucency that forms single compartment.
- *Multilocular type:* It shows number of small, well-defined radiolucent areas giving *honeycomb* or *larger soap-bubble appearance* (this appearance is due to trabeculae pattern and reactionary bone response to the lesion).

Histopathology

The histological patterns of SMA are as follows:

- Follicular SMA
- Plexiform SMA
- Acanthomatous SMA
- Granular cell SMA
- Basal cell SMA

Note: The categorization of these patterns does not have any significance in determining the clinical management or prognosis of the lesion.

Follicular SMA (fig. 4.3)

The tumour consists of islands or follicles of epithelial cells.

- The follicles consist of central stellate reticulum-like cells and peripheral cuboidal or columnar cells with reversal of polarity resembling inner enamel epithelium or preameloblasts.
- Usually, cystic degeneration occurs within these follicles.

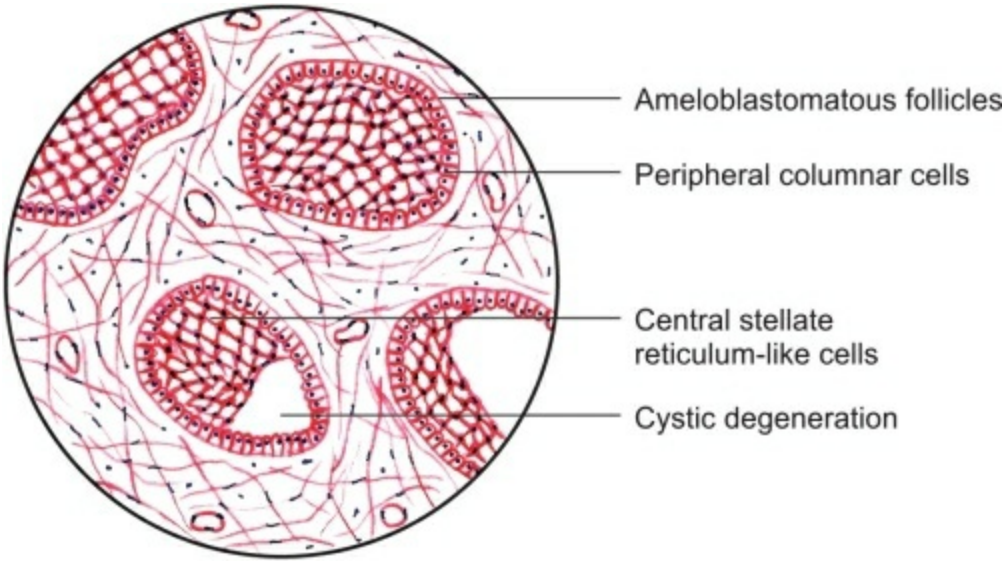


FIG. 4.3 Follicular solid/multicystic ameloblastoma.

Plexiform SMA (plexus: Network) (fig. 4.4)

- The epithelium forms continuous anastomizing strands.
- Tumour epithelium is arranged as a network which is bound by a layer of cuboidal or columnar cells and includes stellate reticulum-like cells.
- Frequently, cyst formation occurs due to stromal degeneration.

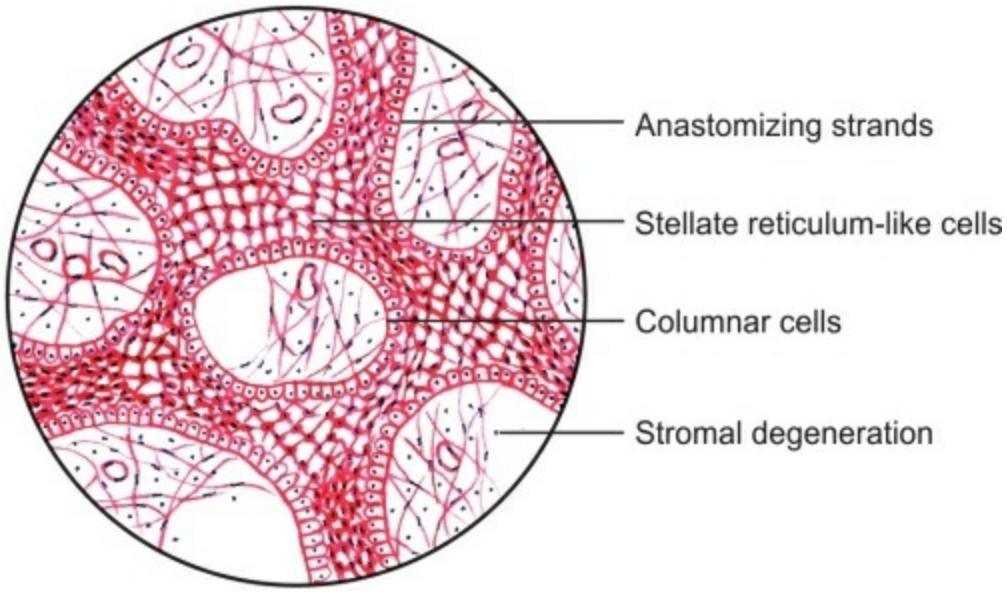


FIG. 4.4 Plexiform solid/multicystic ameloblastoma.

Note: Identification of connective tissue stroma will help to distinguish follicular SMA from plexiform SMA. In follicular SMA, connective tissue stroma will be present within the follicles, whereas in later, it is vice versa.

Acanthomatous SMA (fig. 4.5)

- It shows squamous metaplasia and/or keratin pearl formation within the islands of tumour cells.
- Usually, the general pattern of this tumour is of the follicular type.

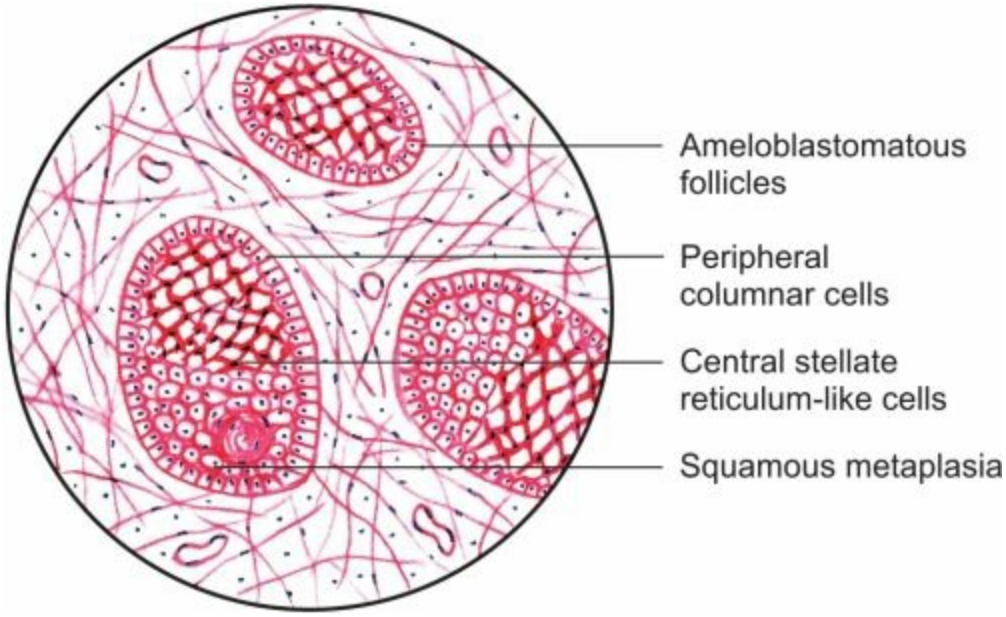


FIG. 4.5 Acanthomatous solid/multicystic ameloblastoma.

Granular cell SMA

- This tumour, most often the follicular type, shows an extensive granular transformation of the central stellate reticulum-like cells. In some lesions, all cells of the tumour islands or nests are composed of granular cells.
- The granular cells can be cuboidal, columnar or round in shape, and cytoplasm is filled with acidophilic granules.
- The cytoplasmic granules have been identified ultrastructurally as lysosomal aggregates that might be caused due to increased apoptotic cell death and associated phagocytosis by neighbouring neoplastic cells.

Basal cell SMA

- The tumour island shows central basaloid and peripheral cuboidal cells.
- No stellate reticulum is present in the central portion of the islands/nests.

Differential diagnosis

- Keratocystic odontogenic tumour
- Dentigerous cyst
- Pindborg's tumour

Prognosis and predictive factors

- Treatment should include excision with an adequate margin of uninvolved tissues.
- Lesions involving the posterior maxilla, demonstrate the poorest prognosis.
- Long-term follow-up is essential, since recurrences have been noted even after 10 years of the initial treatment.

Unicystic ameloblastoma

(Synonym: Cystogenic ameloblastoma)

Definition

The unicystic ameloblastoma (UA) represents an ameloblastoma variant, presenting as a cyst *(WHO, 2005)*.

Pathogenesis

- Reduced enamel epithelium undergoing ameloblastic transformation with subsequent cyst development.
- Ameloblastoma arises in a dentigerous cyst or other types of odontogenic cysts.
- Solid ameloblastoma undergoes cystic degeneration.
- *de novo* (on its own) cystic neoplasm.

Clinical features

- **Age.** 20–30 years.
- **Gender.** No sex predilection.
- **Location.** Posterior region of the mandible.
- **Signs and symptoms**

- Usually most of the lesions are asymptomatic.
- Painless, localized swelling of the jaws and lip numbness are seen.
- Pain and discharge are seen among secondarily infected lesions.

Radiographic features

- It appears as a well-circumscribed unilocular radiolucency with sclerotic border.
- Usually, associated with impacted mandibular third molar tooth.

Histopathology

The unicystic ameloblastoma is of three distinct types (Fig. 4.6):

1. Luminal unicystic ameloblastoma
 - Epithelial lining shows cuboidal or columnar basal cells with hyperchromatic, palisading and polarized nucleus. Cytoplasmic vacuolization, intercellular spacing and subepithelial hyalinization are also seen (*Vickers and Gorlin criteria*).
 - The overlying epithelial cells resemble stellate reticulum.
2. Intraluminal unicystic ameloblastoma
 - One or more nodules of epithelial lining project into the cystic lumen.
 - Sometimes the nodule projecting into the lumen shows a plexiform pattern—*plexiform unicystic ameloblastoma*.
3. **Intramural unicystic ameloblastoma:** In this type, the fibrous wall of the cyst is infiltrated by islands of follicular or plexiform ameloblastoma.

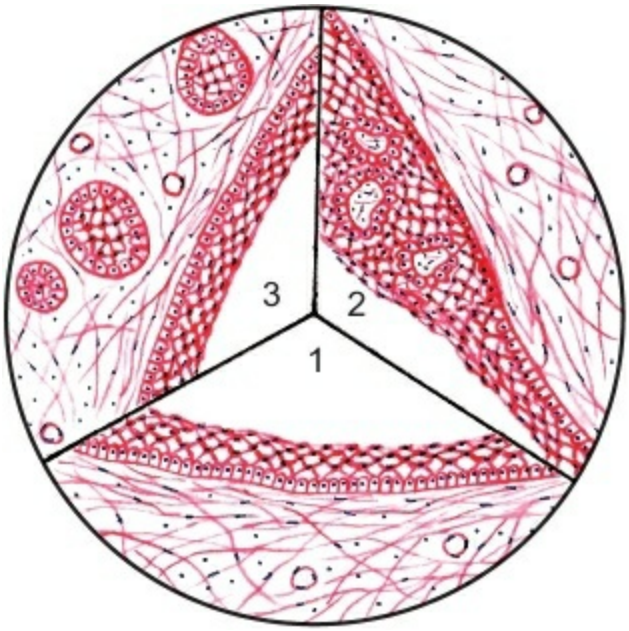


FIG. 4.6 Unicystic ameloblastoma: 1. Luminal unicystic ameloblastoma. 2. Intraluminal unicystic ameloblastoma. 3. Intramural unicystic ameloblastoma.

Differential diagnosis

- Odontogenic keratocyst
- Dentigerous cyst
- Calcifying epithelial odontogenic cyst

Prognosis and predictive factors

- Usually, enucleation is the treatment of choice.
- The luminal variant does not infiltrate into the surrounding bone, so no further treatment is required.
- The mural variant is excised and further treatment depends upon the depth of epithelial invasion into the cyst wall.
 - Limited invasive lesions—careful follow-up
 - Deep invasive lesions—surgical intervention with long-term follow-up

Peripheral ameloblastoma

(Synonyms: Soft tissue ameloblastoma; ameloblastoma of the gingiva)

Definition

The extraosseous/peripheral ameloblastoma (PA) is the extraosseous counterpart of the intraosseous solid/multicystic ameloblastoma (*WHO,*

2005).

Pathogenesis

- Remnants of odontogenic epithelium
- Basal cell off-shouts (hamartias) of gingival epithelium

Clinical features

- **Age.** 30–40 years.
- **Gender.** No sex predilection.
- **Location.** Soft tissues overlying the tooth bearing areas of mandible.
- **Signs and symptoms**
 - It appears as a painless, nonulcerated sessile or pedunculated mass.
 - Clinically, it resembles as fibroma or pyogenic granuloma.

Radiographic features

- Usually, no evidence of radiographic appearance is seen.
- Sometimes, superficial erosion of the bone (cupping or saucerization) may be seen.

Histopathology

- Lesion shows islands of ameloblastic epithelium in the lamina propria underneath the surface epithelium.
- The proliferating epithelium shows features of follicular or plexiform intraosseous ameloblastoma.

Differential diagnosis

- Peripheral odontogenic fibroma
- Peripheral variant of the squamous odontogenic tumour
- Odontogenic gingival epithelial hamartoma

Prognosis and predictive factors

- PA does not show invasive behaviour and conservative excision is the treatment of choice.
- The recurrence rate is low.
- Long-term follow-up is recommended.

Desmoplastic ameloblastoma

Definition

Desmoplastic ameloblastoma (DA) is characterized by an unusual histomorphology with extensive stromal collagenization or desmoplasia; hence the tumour is named as *desmoplastic ameloblastoma (WHO, 2005).*

Pathogenesis

Similar to solid/multicystic ameloblastoma.

Clinical features

- **Age.** 40–50 years.
- **Gender.** Male predilection.
- **Location.** Anterior region of the mandible.
- **Signs and symptoms.** It presents as an asymptomatic painless swelling.

Radiographic features

- It shows mottled, mixed radiolucency or radiopacity with diffuse margins (suggesting a fibro-osseous lesion).
- Resorption of tooth roots is commonly seen.

Histopathology (fig. 4.7)

- The epithelial tumour islands are often irregular in shape with an almost pathognomic *animal-like configuration*.
- Epithelial cells at the periphery of the islands are cuboidal or columnar in shape, whereas centre of the epithelial islands appears hypercellular with spindle-shaped or squamatoid epithelial cells.
- Extensive stromal desmoplasia (increased fibrosis) seems to compress or squeeze the odontogenic epithelial islands from the periphery.

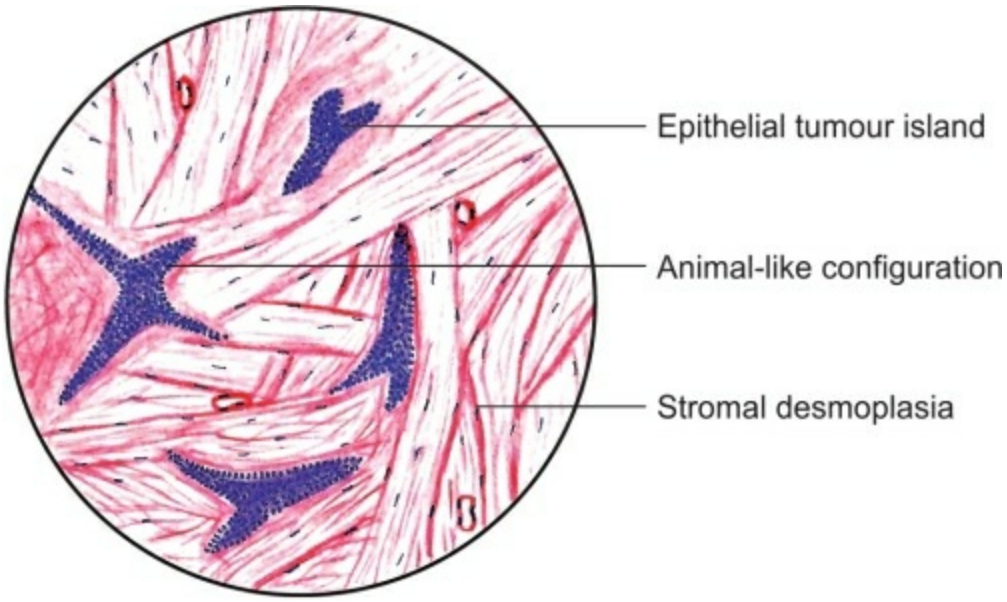


FIG. 4.7 Desmoplastic ameloblastoma.

Note: Usually, DA with areas of follicular or plexiform ameloblastoma is called as *hybrid lesion of ameloblastoma*.

Differential diagnosis

- Odontogenic keratocyst
- Dentigerous cyst
- Central giant cell granuloma

Prognosis and predictive factors

Surgical excision with an adequate margin of uninvolved tissues is recommended.

Adenomatoid odontogenic tumour

(Synonyms: Adenoameloblastoma; ameloblastic adenomatoid tumour)
In 1969, Philipsen and Birn introduced the term *adenomatoid odontogenic tumour* (AOT). Till then it is known as *adenoameloblastoma*.

Definition

Adenomatoid odontogenic tumour is a benign hamartomatous lesion,

composed of odontogenic epithelium in a variety of histoarchitectural patterns, embedded in a mature connective tissue stroma and characterized by slow but progressive growth *(WHO, 2005)*.

Pathogenesis

- Derived from dental lamina or its remnants
- Disturbances during presecretory stage of enamel organ

Clinical features

AOT occurs in two forms:

1. Central/intraosseous variant.
2. Peripheral/extraosseous variant.
 - **Age.** 20–30 years.
 - **Gender.** Female predilection.
 - **Location.** Anterior region of the maxilla—both central and peripheral variants.
 - **Signs and symptoms**
 - It appears as slow growing, bony hard swelling which is often associated with unerupted upper canine.
 - Displacement of the regional teeth, mild pain and expansion of the cortical bones are usually seen.
 - The extraosseous variant produces a solitary, painless, asymptomatic nodular gingival swelling.

Radiographic features

- Intrabony variant occurs as a unilocular radiolucency with a smooth corticated border.
- About two-thirds of the intrabony variants show radiopaque foci within the radiolucent lesion.
- The peripheral variants may show saucerization of the alveolar bone crest.
- Radiographic variants are as follows (Fig. 4.8):
 1. *Intraosseous follicular type (F)*: It is located around the crown and often covers part of the root of an unerupted tooth (envelopmental type).
 2. *Extraosseous follicular types (E)*
 - E1: No relation to tooth structures.
 - E2: Interradicular, adjacent roots diverge apically due to tumour

expansion.
- E3: Superimposed on root apex.
- E4: Superimposed on mid-third of the root.

3. *Extraosseous peripheral type (P):* It exhibits slight erosion of the alveolar bone crest.

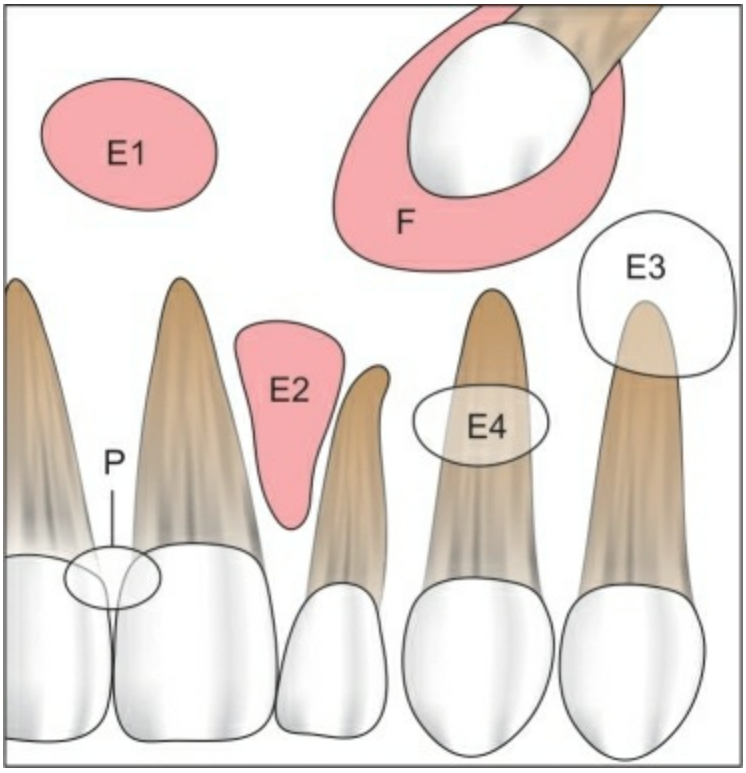


FIG. 4.8 Radiographic variants of AOT.

Histopathology (fig. 4.9)

It shows a combination of the following patterns:

- **Rosette pattern:** It is composed of cuboidal or columnar epithelial cells forming rosette-like structures with minimal mature fibrous connective tissue stroma. Between the epithelial cell nodules and in the centre of rosette-like configuration, amorphous eosinophilic material (tumour droplets) is present.
- **Tubular or ductal pattern** (hence the name *adenomatoid gland like*): It shows duct-like spaces lined by a single row of cuboidal cells with empty or amorphous material in the lumen.
- **Solid pattern:** It is composed of varying size nodules exhibiting well-

defined squamous cell with prominent intercellular bridges. These nodules may contain pools of amorphous eosinophilic material and globular masses of calcified substances.

- **Trabecular or cribriform pattern:** It is composed of one to two cells thickness interconnecting epithelial strands. Usually, this pattern is seen at periphery of the tumour.
- Sometimes a *whorled pattern* with a thin layer of tumour droplets between opposing rows of columnar cells is seen.
- Spindle-shaped cells are seen between these epithelial structures.
- In some cases, AOT may occur with CEOT (combined epithelial odontogenic tumours).
- Hyaline, dysplastic dentinoid material or calcified osteodentine can also occur in some areas of tumour.

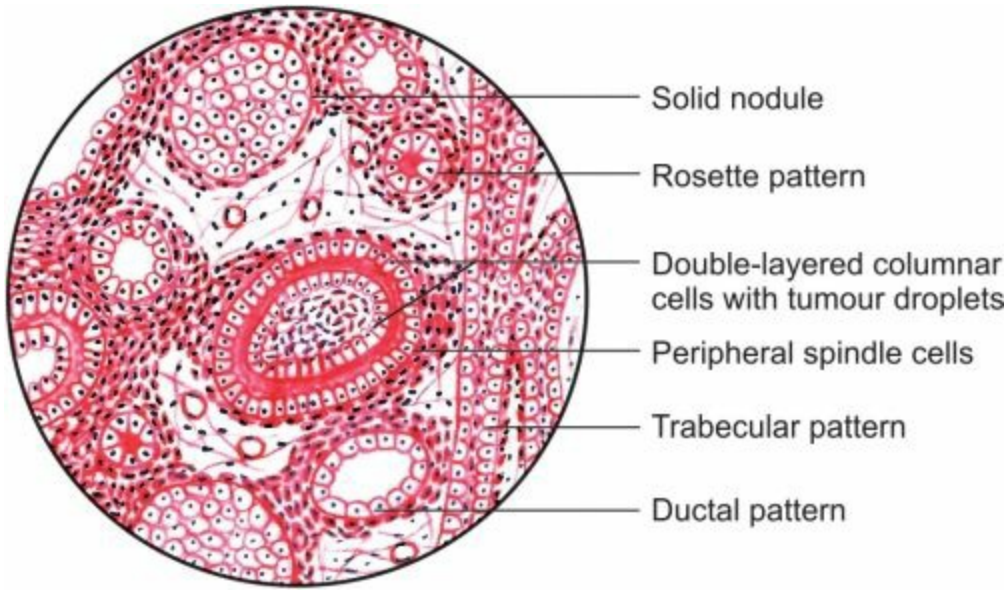


FIG. 4.9 Adenomatoid odontogenic tumour.

Differential diagnosis

- Dentigerous cyst
- Globulomaxillary cyst
- Lateral periodontal cyst

Prognosis and predictive factors

- AOTs are cured by local excision.

- Recurrences are extremely rare.

Squamous odontogenic tumour

Definition

It is a locally infiltrating neoplasm consisting of islands of well-differentiated squamous epithelium in a fibrous stroma *(WHO, 2005).*

Pathogenesis

- Remnants of odontogenic epithelium
- Hamartias

Clinical features

- **Age.** 20–30 years.
- **Gender.** Male predilection.
- **Location**
 - Maxilla: incisor–cuspid area.
 - Mandible: molar–bicuspid area.
- **Signs and symptoms**
 - Asymptomatic lesion often develops from periodontal ligament of permanent teeth.
 - Slow-growing swelling, mobility of teeth and moderate pain may be present.

Radiographic features

Well-defined unilocular, triangular radiolucency is seen between the roots of adjacent teeth.

Histopathology (fig. 4.10)

- It is composed of round or oval-shaped islands of well-differentiated squamous epithelium.
- Individual tumour islands reveal a peripheral layer of low cuboidal or even flat epithelial cells.
- The central squamous cells are very uniform in size and they do not exhibit pleomorphism, nuclear hyperchromatism or mitotic activity.
- Sometimes, individual epithelial islands may undergo central microcystic

degeneration following single-cell keratinization.

- Few islands may enlarge and contain laminar calcified material.
- Globular eosinophilic material can be seen within the islands, which are not amyloid.

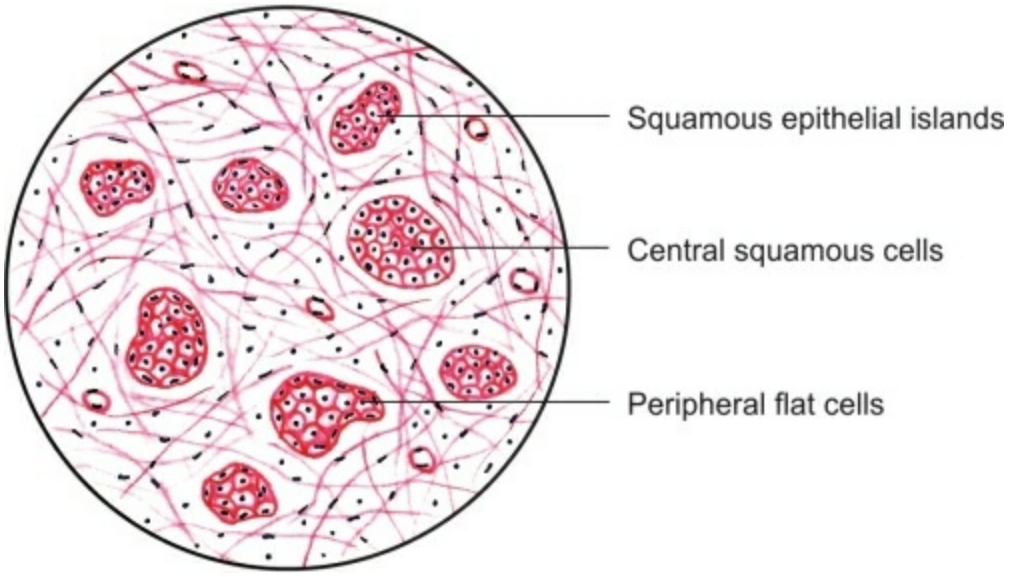


FIG. 4.10 Squamous odontogenic tumour.

Differential diagnosis

- Lateral periodontal cyst
- Ameloblastoma (acanthomatous pattern)
- Squamous cell carcinoma

Prognosis and predictive factors

- Conservative surgical treatment is usually sufficient.
- Recurrences are rare.

Calcifying epithelial odontogenic tumour

(Synonym: Pindborg tumour)

The calcifying epithelial odontogenic tumour (CEOT) was first reported by Pindborg in 1955, hence the eponym *Pindborg tumour.*

Definition

It is a locally invasive epithelial odontogenic neoplasm, characterized by the presence of amyloid material that may become calcified *(WHO, 2005).*

Pathogenesis

It may arise from:

- Reduced enamel epithelium
- Cell rests of Serre or hamartias

Clinical features

CEOT occurs in two forms:

1. Central/intraosseous variant
2. Peripheral/extraosseous variant
 - **Age.** 20–60 years.
 - **Gender.** Male predilection.
 - **Location.** Posterior region of mandible.
 - **Signs and symptoms**
 - *Intraosseous lesion* presents as a painless, slow-growing swelling, often associated with unerupted tooth.
 - Usually, maxillary central lesions produce nasal congestion, epistaxis and headache.
 - *Extraosseous lesion* presents as a painless, firm gingival mass, often resembles pyogenic granuloma.

Radiographic features

- Usually, intraosseous lesions show irregular unilocular or multilocular radiolucent areas containing radiopaque masses of varying sizes, which give a characteristic *snow-driven appearance*.
- The peripheral lesion sometimes causes saucerization of the underlying bone.

Histopathology (fig. 4.11)

- The basic histologic pattern of CEOT includes variable combination of odontogenic epithelium and calcified structures.
- The tumour epithelium is composed of polyhedral epithelial cells with prominent intercellular bridges either arranged in a closely packed in large sheets or as a scattered small islands in a bland fibrous connective tissue stroma.

- The nuclei are frequently pleomorphic, but mitotic figures are rare.
- *Clear cell variant:* In this type, the tumour cells exhibit a clear vacuolated cytoplasm rather than an eosinophilic cytoplasm. The nucleus may be round or oval in shape, which will be present at the centre of the cell or flattened against the basement membrane.

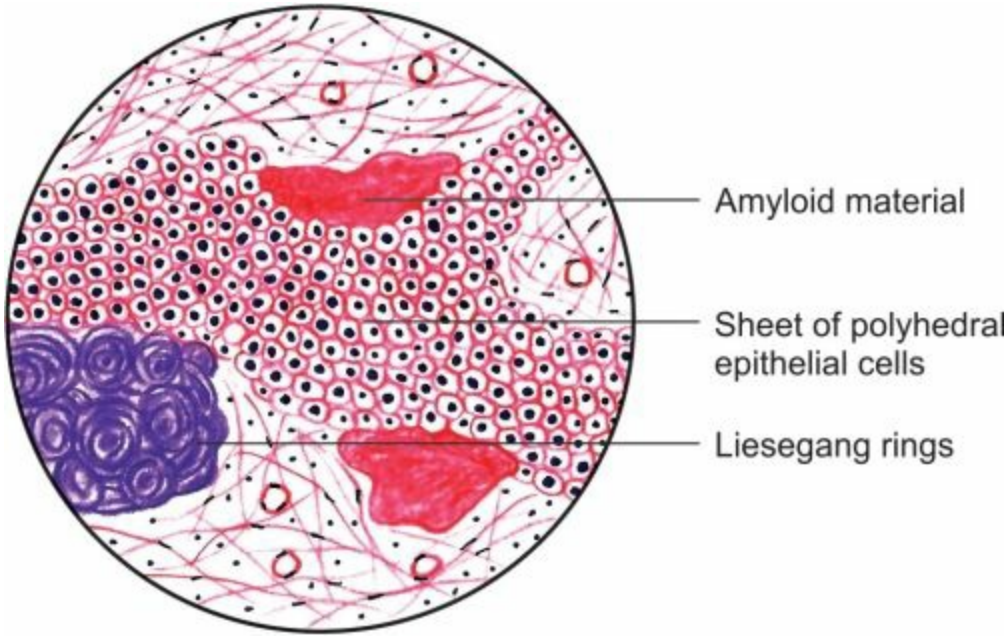


FIG. 4.11 Calcifying epithelial odontogenic tumour.

Amyloid material of CEOT

A homogenous, eosinophilic substance which stains metachromatically with crystal violet, positively with Congo red and fluoresces under ultraviolet light with thioflavin T in a fashion similar to amyloid. However, the exact nature of amyloid substance in CEOT is still not known.

Calcifications in CEOT

- Usually, classifications occur as dark hematoxyphilic concentrically laminated calcified masses—*Liesegang rings.*
- Sometimes, these may occur in the form of globules.

Cementum-like components in CEOT

- These occur as well-circumscribed darkly staining hematoxyphilic

globules in the connective tissue stroma.
- The mechanism of formation is still unclear, but these are thought to be dystrophic calcifications.
- *Slootweg (1991)* suggested that the amyloid-like material is an inductive stimulus for the stromal cells to differentiate towards production of a collagenous matrix that is destined to mineralize and resemble cementum.

Differential diagnosis

- Calcifying epithelial odontogenic cyst
- Adenomatoid odontogenic tumour
- Intraosseous squamous cell carcinoma

Prognosis and predictive factors

- It is a locally invasive tumour. Small tumours may be enucleated, but larger lesions require local resection.
- Long-term follow-up is recommended.

Keratocystic odontogenic tumour (KCOT)

This topic is discussed in Chapter 5 *Cysts of the Oral and Maxillofacial Regions*.

Ameloblastic fibroma

(Synonym: Fibroadamantoblastoma)

Definition

Ameloblastic fibroma (AF) consists of odontogenic ectomesenchyme resembling the dental papilla and epithelial strands and nests resembling dental lamina and enamel organ. No dental hard tissues are present. If there is dentine formation, the lesion is referred to as *ameloblastic fibrodentinoma (WHO, 2005).*

Pathogenesis

It may arise from the normal tooth anlage before the primitive induction of ectomesenchymal cells for hard tissue formation.

Clinical features

- **Age.** 10–20 years.
- **Gender.** Male predilection.
- **Location.** Posterior region of the mandible.
- **Signs and symptoms**
 - It occurs as a painless, slow-growing expansile lesion.
 - Usually, lesions are identified during routine radiographic examination.

Radiographic feature

It appears as a well-defined unilocular or multilocular radiolucency with a sclerotic border.

Histopathology

- It consists of epithelial and ectomesenchymal component.
- Epithelial component is composed of proliferating odontogenic epithelium arranged in the form of islands and strands.
- Islands show peripheral cuboidal or columnar cells with central stellate reticulum-like cells.
- Strands often reveal as a double or triple layer of cuboidal cells including stellate reticulum-like cells.
- Ectomesenchymal component includes rounded or angular-shaped cells with few delicate collagen fibrils.

Differential diagnosis

- Ameloblastoma
- Calcifying odontogenic cyst
- Dentigerous cyst

Prognosis and predictive factors

- Treatment consists of enucleation and curettage.
- Recurrence may occur but this does not justify initial aggressive treatment.
- Rarely, AF may progress to malignancy (ameloblastic fibrosarcoma).

Ameloblastic fibrodentinoma

Definition

Ameloblastic fibrodentinoma (AFD) is a neoplasm similar to ameloblastic fibroma, but also showing inductive changes that lead to formation of dentine *(WHO, 2005).*

Pathogenesis

AFD may be an intermediate stage in the pathogenesis of ameloblastic fibro-odontoma.

Clinical features

- **Age.** 10–20 years.
- **Gender.** Male predilection.
- **Location.** Posterior region of the mandible.
- **Signs and symptoms**
 - Slow growing, often asymptomatic tumour which may become quite larger in size.
 - It may be associated with unerupted teeth in few cases.

Radiographic features

It appears as a well-circumscribed radiolucency with varying degrees of radiopacity depending upon amount of dentine production.

Histopathology (fig. 4.12)

- AFD consists of epithelial and ectomesenchymal components similar to AF.
- Osteodentine (dentine with entrapped odontoblasts), dentinoid (atubular dentine-like) or tubular dentine structures are also seen.

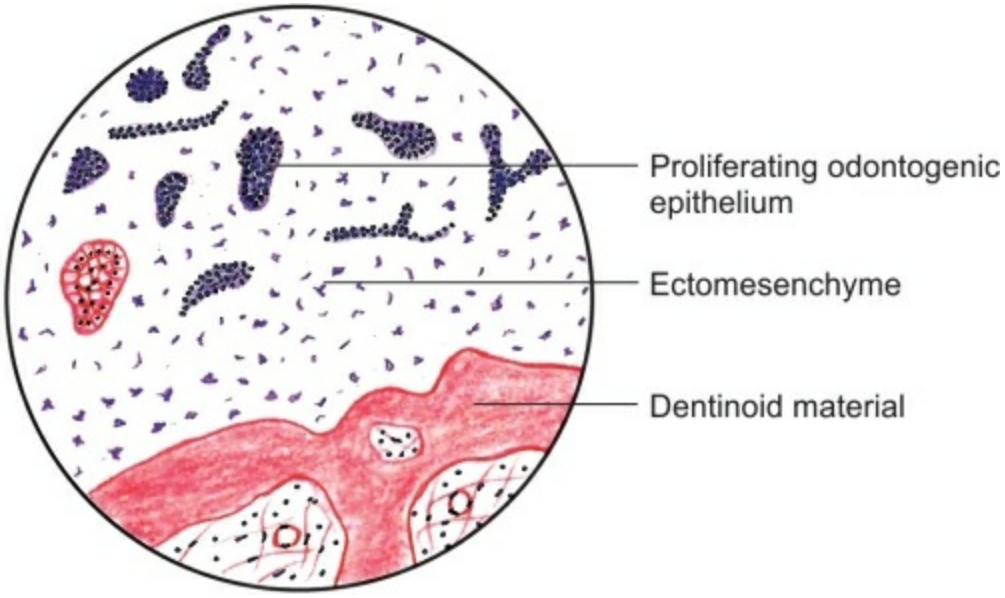


FIG. 4.12 Ameloblastic fibrodentinoma.

Prognosis and predictive factors

- Treatment consists of enucleation and curettage.
- Recurrence may occur but this does not justify initial aggressive treatment.
- Rarely, AFD may progress to malignancy (ameloblastic fibrodentinosarcoma).

Ameloblastic fibro-odontoma

Definition

Ameloblastic fibro-odontoma (AFO) is a tumour, which has the histologic features of ameloblastic fibroma (AF) in conjunction with the presence of dentine and enamel *(WHO, 2005).*

Pathogenesis

- Unknown.
- *Continuum concept of Cahn and Blum:* Cahn and Blum proposed that AF over time matures to form AFD and AFO and finally results in the formation of an odontoma.
- Reasons for nonacceptance of this theory are as follows:
 - Recurrent or residual cases of AF have never shown further steps of

differentiation or maturation into a dental hard tissue.
- AF is known to occur at age group beyond completion of odontogenesis.
- Age distribution—AF: 10–20 years; AFD: 10–20 years; AFO: <10 years.

Clinical features

- **Age.** <10 years.
- **Gender.** Male predilection.
- **Location.** Posterior region of the mandible.
- **Signs and symptoms**
 - Well circumscribed, painless, slow-growing lesion with no propensity for bone invasion.
 - Majority of the cases are associated with unerupted tooth.

Radiographic features

- It occurs as a unilocular or multilocular radiolucency with a sclerotic border.
- The central part of the lesion shows irregular or rounded homogenous radiopaque calcified masses.

Histopathology

- It shows irregularly arranged enamel, dentine, cementum and pulp-like ectomesenchymal tissues.
- Dentine may vary structurally from dentinoid to tubular dentine.
- Amount of ectomesenchyme gradually decreases as the hard tissue mass dominates in the central part of the lesion.

Prognosis and predictive factors

- Surgical excision is advised.
- The prognosis is good.
- Recurrence is rare.

Odontomas

- Odontomas are the most common odontogenic tumours.
- Odontoma is a mixed odontogenictumour composed of both epithelial and ectomesenchymal components.
- In odontomas, epithelial and ectomesenchymal tissues and their

respective cells may appear normal morphologically, but they seem to have a deficit in structural arrangement. This defect has led to opinion that odontomas are *hamartomatous lesions* or *malformations* rather than a true neoplasm.

- There are two types of odontomas:
 1. **Complex odontoma:** Dental tissues are well arranged.
 2. **Compound odontoma:** Dental tissues are disorderly arranged.

Aetiology

Unknown, but several hypotheses have been proposed including:

- Local trauma
- Infection
- Family history
- Genetic mutation

Pathogenesis

- It is a self-limiting developmental anomaly or hamartomatous malformation found as nondescript masses of dental tissues.
- Factors that cause anomalous tissue development in odontomas are:
 - Altered ectomesenchymal interaction during tooth development.
 - Alteration in the mineralization mechanisms.

Complex odontomas

Definition

Malformation in which all the dental tissues are represented, individual tissues being mainly well formed but occurring in a more or less disorderly pattern *(WHO, 2005).*

Clinical features

- **Age.** 10–20 years.
- **Gender.** Male predilection.
- **Location.** Posterior region of the mandible.
- **Signs and symptoms**
 - It appears as round or ovoid shaped, slow growing, painless swelling.
 - Usually, size of the lesion ranges from 3 to 4 cm in diameter.

- Often detected during routine radiographic examination for unerupted tooth or retained deciduous tooth.

Radiographic features

It depends on developmental stage of the lesion:

- *1st stage*: Radiolucent lesion is seen due to lack of calcification (Weiches odontoma).
- *2nd stage*: Partial calcification is seen.
- *3rd stage*: Radiopaque mass of dental hard tissues surrounded by a thin radiolucent zone is seen.

Histopathology (fig. 4.13)

- It consists of a disordered mixture of dental tissues, often spherical in shape.
- Cementum-like structures often admixed with the dentinoid substance, small spaces with pulp tissue, enamel matrix and epithelial remnants are seen.
- Empty spaces and clefts are caused due to loss of enamel during the process of decalcification.
- A thin, fibrous capsule is seen surrounding the lesion.
- Sometimes complex odontomas show areas of ghost cells.

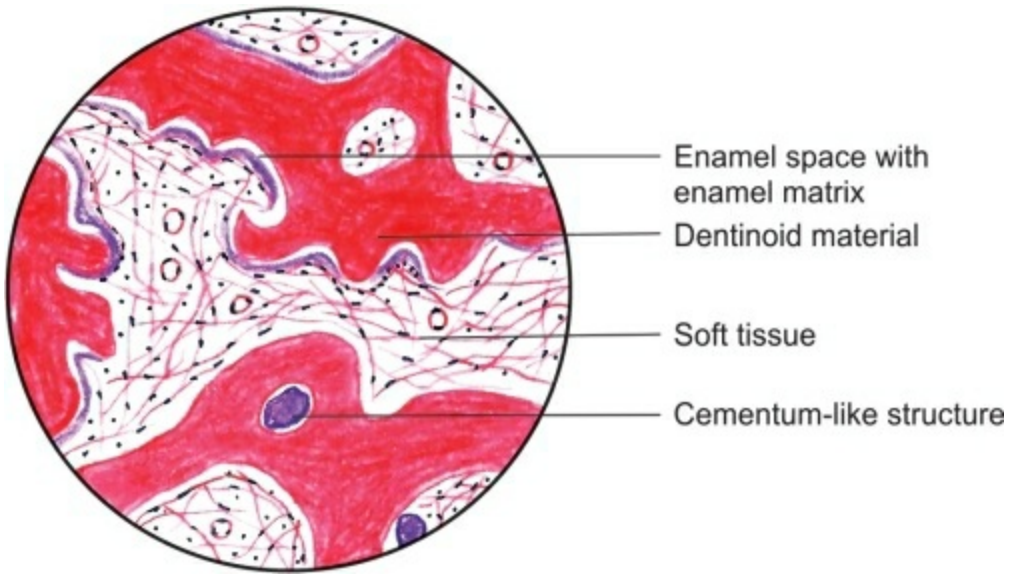


FIG. 4.13 Complex odontoma.

Prognosis and predictive factors

- Complex odontomas are treated by local excision.
- Recurrence is rarely reported.

Compound odontomas

Definition

A malformation in which all the dental tissues are represented in a more orderly pattern than in the complex odontoma, so that the lesion consists of many tooth-like structures. Most of these structures do not morphologically resemble the teeth of the normal dentition, but in each structure, enamel, dentine, cementum and pulp are arranged as in normal tooth *(WHO, 2005).*

Clinical features

- **Age.** 10–20 years.
- **Gender.** No sex predilection.
- **Location.** Anterior region of the maxilla.
- **Signs and symptoms**
 - It is a painless, slow-growing lesion with a limited growth potential than complex odontomas.
 - Growth potential ends with the tooth-forming period.
 - Often detected during routine radiographic examination for unerupted tooth or retained deciduous tooth.
 - Compound odontomas may be associated with *Gardner's syndrome.*

Radiographic features

- It comprises a radiopaque mass with number of teeth-like structures arranged in a disorderly fashion.
- These denticles are miniaturized and malformed.
- The lesion is surrounded by a narrow radiolucent rim corresponding to a fibrous capsule at periphery.

Histopathology (fig. 4.14)

- It is composed of denticles showing enamel, dentine, cementum and pulp tissues in a regular arrangement.
- Higher degree of morphodifferentiation is seen.

- Usually small, but large lesions contain up to 100 denticles.
- The lesion is often surrounded by a thick fibrous capsule.
- 3% of odontomas may contain ghost cells.

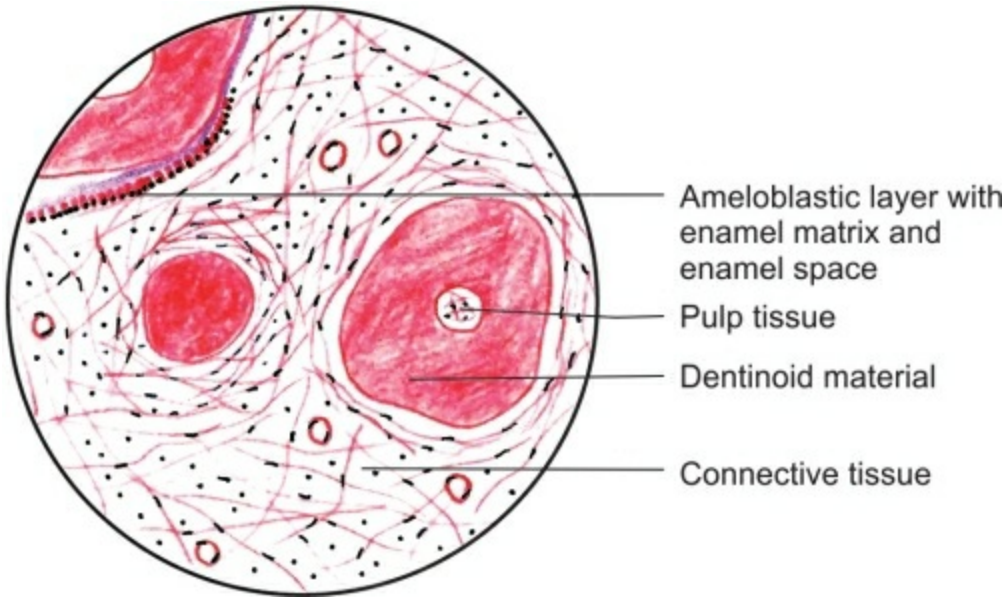


FIG. 4.14 Compound odontoma.

Differential diagnosis

- Calcifying epithelial odontogenic tumour
- Ameloblastic fibro-odontoma
- Osteoma

Prognosis and predictive factors

- Compound odontomas are treated by local excision.
- Recurrence is rarely reported.

Odontogenic fibroma

Definition

The odontogenic fibroma (OF) is a rare neoplasm characterized by varying amounts of inactive-looking odontogenic epithelium embedded in a mature, fibrous stroma *(WHO, 2005)*.

Pathogenesis

- Ectomesenchymal tissue of dental papilla or dental follicle
- Rests of the dental lamina

Clinical features

- **Age.** 30–40 years.
- **Gender.** Female predilection.
- **Location**
 - Mandible—molar and premolar regions.
 - Maxilla—anterior region.
- **Signs and symptoms**
 - Painless, slow growing but progressive lesion with frequent cortical bone expansion is seen.
 - Mobility of teeth may be present in lesional area.

Radiographic features

- Not diagnostic, however, unilocular radiolucent area with well-defined sclerotic border is seen.
- Larger lesions show scalloping of the margins or multiloculation.

Histopathology

It occurs in two forms:

1. **Simple-type central odontogenic fibroma**
 - It is characterized by mature collagen fibres interspersed with plump fibroblasts that are uniformly arranged.
 - Small nests or islands of odontogenic epithelium may be present in minimal amounts.
2. **WHO-type central odontogenic fibroma**
 - It consists of a cellular fibrous connective tissue with some odontogenic epithelial islands.
 - Osteoid, dysplastic dentine or cementum-like structures may also present.

Differential diagnosis

- CEOT
- Ameloblastoma
- Cemento-ossifying fibroma

Prognosis and predictive factors

It can be treated by local enucleation.

Odontogenic myxoma or myxofibroma

(Synonym: Odontogenic fibromyxoma)

Definition

Odontogenic myxoma (OM) is an intraosseous neoplasm characterized by stellate and spindle-shaped cells embedded in an abundant myxoid or mucoid extracellular matrix. When a relatively greater amount of collagen is evident, the term 'myxofibroma' may be used *(WHO, 2005).*

Pathogenesis

The dental papilla, dental follicle and periodontal tissues have been implicated as possible germ centres for OM.

Clinical features

- **Age.** 20–40 years.
- **Gender.** Female predilection.
- **Location.** Posterior region of the mandible.
- **Signs and symptoms**
 - It occurs as a slow-growing painless swelling with displacement of teeth in the lesional area.
 - Maxillary lesion fills entire antrum and causes nasal obstruction or exophthalmos.

Radiographic features

- It shows multilocular radiolucency with a *soap-bubble* or *honeycombappearance*.
- Resorption of roots may be seen.

Histopathology (fig. 4.15)

- OM is a locally aggressive, nonencapsulated, nonmetastasizing neoplasm that often infiltrates into adjacent bone marrow spaces.
- It is characterized by abundant loose fibrillar mucoidstroma that usually contains round, spindle or angular-shaped cells.

- Cellular and nuclear pleomorphism is rare.
- Stroma may be relatively avascular or may exhibit delicate capillaries.
- In case of myxofibroma—the amount of collagen in the mucoidstroma is more prominent.

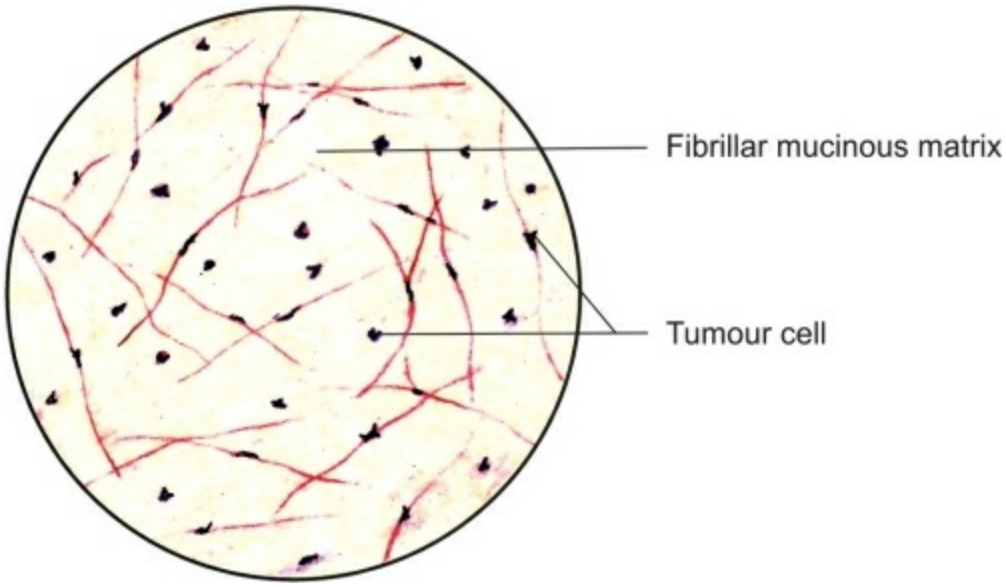


FIG. 4.15 Odontogenic myxoma.

Differential diagnosis

- Central giant cell granuloma
- Aneurysmal bone cyst
- Chondromyxoid fibroma

Prognosis and predictive factors

- The tendency of OM to permeate into marrow spaces makes effective enucleation or curettage difficult.
 - Small lesions—enucleation or curettage
 - Larger lesions—complete excision with tumour-free margins
- Recurrence usually follows incomplete removal.
- Death may ensue due to cranial base extension.

Cementoblastoma

(Synonym: True cementoma)

Cementoblastoma is the only true neoplasm of cemental origin and usually characterized by the proliferation of cellular cementum.

Definition

A cementoblastoma is characterized by the formation of cementum-like tissue in connection with the root of a tooth *(WHO, 2005).*

Pathogenesis

- It may arise from the ectomesenchymal cells of periodontium.
- It is considered as a neoplasm with unlimited growth potential.
- It forms in three stages:
 - *1st stage:* Peripheral osteolytic stage
 - *2nd stage:* Cementoblastic stage
 - *3rd stage:* Maturation and calcification stage

Clinical features

- **Age.** 20–30 years.
- **Gender.** Female predilection.
- **Location.** In relation to mandibular permanent molar and premolars.
- **Signs and symptoms**
 - It presents as a slow-growing, unilateral swelling with cortical bone expansion.
 - Lesions are commonly associated with tooth roots.
 - Pain—similar to toothache arising in the pulp, is commonly present.

Radiographic features

- It appears as a radiopaque, round mass fused with one or several roots of associated teeth, thus obliterating the radiopaque details of root(s).
- Opacity is often surrounded by a thin, well-defined radiolucent border.

Histopathology

- *Cemental tubercle or mass:* Dark basophilic, round or oval-shaped structure with numerous reversal lines.
- The periphery of the lesion is rimmed with plump, active cementoblasts and cementoclasts.
- Sometimes, fibrous tissue with dilated blood vessels and multinucleated giant cells may be observed between the calcified bands.

Differential diagnosis

- Osteoblastoma
- Osteoid osteoma
- Focal sclerosing osteomyelitis

Prognosis and predictive factors

It should be excised with the associated tooth, otherwise recurrence is common.

Metastasizing malignant ameloblastoma

Definition

Metastasizing malignant ameloblastoma is an ameloblastoma that metastases in spite of a benign histologic appearance *(WHO, 2005).*

Pathogenesis

- Origin is likely to be same as that of benign ameloblastoma.
- The spread of tumour could result from either due to
 - increasing malignant behaviour stimulated by multiple recurrences or
 - implantation of the tumour into lymphatic or blood vessels by repeated surgical interventions.
- *Factors that appear to contribute for potential metastatic spread*
 - Duration of neoplasm
 - Extent and size of the initial tumour
 - Initial type of surgery (conservative versus radical therapy)
 - Multiple recurrences and respective surgery interventions
- *Most common sites to metastasis:* Lung, hilar lymph node, bones, skull, vertebrae and femur, cervical lymph nodes, liver, brain, other nodes, spleen and kidney.

Clinical features

- **Age.** >50 years.
- **Gender.** Male predilection.
- **Location.** Posterior region of the mandible.
- **Signs and symptoms.** Painful swelling, delayed tooth eruption, ulceration and tooth mobility are the most common symptoms.

Histopathology

- The primary jaw tumour and metastatic deposits show histopathological features similar to conventional ameloblastoma.
- Usually, histopathological patterns of follicular or plexiform ameloblastoma are seen.
- 80% of the lesions occur in pure form.
- It does not show greater cytological atypia or mitotic activity.
- Rarely, necrosis in tumour islands and areas of dystrophic calcification are seen.

Prognosis and predictive factors

Poor prognosis.

Ameloblastic carcinoma

(Synonym: Carcinoma ex ameloblastoma)

Definition

Ameloblastic carcinoma (AC) is a rare primary odontogenic malignancy that combines the histological features of ameloblastoma with cytological atypia. This will be the case even in the absence of metastases *(WHO, 2005).*

Pathogenesis

It may arise as:

- Ex-ameloblastoma or ex-odontogenic cyst
- *de novo* lesion

Clinical features

- **Age.** >50 years.
- **Gender.** Male predilection.
- **Location.** Posterior region of the mandible.
- **Signs and symptoms**
 - Swelling, pain, trismus and dysphonia are evident.
 - Rapid growth of the tumour is an important feature.
 - Commonly, mental nerve paraesthesia is seen.

Radiographic features

- Resembles solid/multicystic ameloblastoma, but in most cases, it presents as ill-defined radiolucencies.
- Foci of radiopacities probably due to dystrophic calcification are observed.

Histopathology

- It is composed of islands and cords of ameloblastomatous odontogenic epithelium in an infiltrating pattern within the stroma of mature fibrous tissue.
- *Epithelium component* shows less orderly pattern of peripheral columnar or cuboidal cells with reversal of polarity and central stellate reticulum-like cells.
- Characteristic features of malignant odontogenic epithelium include:
 - Nuclear hyperchromatism.
 - Nuclear enlargement with granular stippled nucleoplasm.
 - Cellular and nuclear pleomorphism.
 - Increased nuclear-cytoplasmic ratio.
 - Increased mitotic activity with abnormal forms of mitoses.
 - Individual cell keratinization and keratin pearl formation.
 - Different histologic patterns may be noted—highly differentiated squamous cell to poorly differentiated basaloid cells.
- *Connective tissue component* composed of mature collagen fibres, necrosis, dystrophic calcifications with occasional inflammatory cells, haemorrhage and/or haemosiderin pigments.
- Rarely, clear cell differentiation is seen in epithelial component.

Prognosis and predictive factors

- Maxillary ameloblastic carcinomas demonstrate tumour-related deaths or pulmonary metastases.
- Mandibular counterparts behave in a similar manner, where local recurrences are likely to precede metastases.

Primary intraosseous squamous cell carcinoma

(Synonym: Primary intra-alveolar epidermoid carcinoma)

Definition

Primary intraosseous squamous cell carcinoma (PIOSCC) is a central jaw

carcinoma derived from odontogenic epithelial remnants. Subcategories of PIOSCC include:

1. A solid tumour that invades marrow spaces and induces osseous resorption.
2. Squamous cancer arising from the lining of an odontogenic cyst.
3. A squamous cell carcinoma in association with other benign epithelial odontogenic tumours.

When the tumour destroys the cortex and merges with the surface mucosa, it may be difficult to distinguish between a PIOSCC and a true carcinoma arising from the oral mucosa *(WHO, 2005).*

Pathogenesis

It may arise from:

- Reduced enamel epithelium or remnants of odontogenic epithelium.
- Transformation of odontogenic cysts and tumours like KCOT, dentigerous cyst.

Clinical features

- **Age.** >50 years.
- **Gender.** Male predilection.
- **Location.** Posterior region of the mandible.
- **Signs and symptoms**
 - Persistent post-extraction pain, toothache, periodontal disease, pericoronitis, sensory disturbances or swelling are the common presenting symptoms.
 - The diagnosis has to be considered in cases where initial dental treatment has failed.

Radiographic feature

Diffuse radiolucency with poorly defined irregular margins is seen.

Histopathology

- It shows distinct odontogenic pattern with basal cells arranged in an alveolar or plexiform pattern with palisading arrangement at the periphery.
- Squamous metaplasia and keratinization may be seen.
- Few cases show foci of degeneration within epithelial islands.

- Since histopathology of PIOSCC is not pathognomonic, a diagnosis can be made only if there is no evidence of the tumour arising from either the oral mucosa or from odontogenic cysts.

Prognosis and predictive factors

Poor prognosis.

Ameloblastic fibrosarcoma

(Synonym: Ameloblastic sarcoma)

Definition

Ameloblastic fibrosarcoma (AFS) is an odontogenic tumour with a benign epithelial and a malignant ectomesenchymal component. It is regarded as the malignant counterpart of the ameloblastic fibroma (AF) *(WHO, 2005).*

Pathogenesis

Transformation of AF to AFS

Clinical features

- **Age.** >50 years.
- **Gender.** Male predilection.
- **Location.** Posterior region of the mandible.
- **Signs and symptoms**
 - Painful swelling is the common symptom.
 - Ulceration, bleeding, mobility of teeth and paraesthesia of the lower lip may also occur.

Radiographic features

Multilocular radiolucency with gross expansion and thinning of cortical bone is seen.

Histopathology

- It is characterized by a malignant ectomesenchymal component with benign epithelial component.
- *Malignant ectomesenchymal component* shows numerous pleomorphic

fibroblast-like cells with hyperchromatic nuclei and increased atypical mitotic activity.
- AFS can demonstrate focal evidence of dentine or combination of dentine and enamel— *ameloblastic fibrodentinosarcoma* or *ameloblastic fibro-odontosarcoma*, respectively.
- *Benign epithelial component* shows epithelial islands, nests or chords with the same histopathological appearance as ameloblastic fibroma.

Prognosis and predictive factors

- Surgical resection is the treatment of choice.
- Ameloblastic sarcomas seem to have a better prognosis than other jaw sarcomas and can generally be regarded as low-grade tumours.

Key points

- *Ameloblastoma* is defined as usually unicentric, nonfunctional, intermittent in growth, anatomically benign and clinically persistent.
- Ameloblastoma shows histological patterns like follicular, plexiform, acanthomatous, granular cell and basal cell pattern.
- *Adenomatoid odontogenic tumour* is a benign hamartomatous lesion, composed of odontogenic epithelium in a variety of histoarchitectural patterns, embedded in a mature connective tissue stroma and characterized by slow but progressive growth.
- *Squamous odontogenic tumour* is a locally infiltrating neoplasm consisting of islands of well-differentiated squamous epithelium in a fibrous stroma.
- *Calcifying epithelial odontogenic tumour* is a locally invasive epithelial odontogenic neoplasm characterized by the presence of amyloid material that may become calcified.
- *Ameloblastic fibroma* consists of odontogenic ectomesenchyme resembling the dental papilla and epithelial strands and nests resembling dental lamina and enamel organ.
- *Odontomas* are the most common odontogenic tumours.
- *Complex odontoma*: Dental tissues are well arranged.
- *Compound odontoma:* Dental tissues are disorderly arranged.
- *Metastasizing malignant ameloblastoma* is an ameloblastoma that metastasizes in spite of a benign histologic appearance.
- *Ameloblastic carcinoma* is a rare primary odontogenic malignancy that combines the histological features of ameloblastoma with cytological

atypia and absence of metastases.

Frequently asked questions

1. Classify odontogenic tumours of the jaws and discuss the pathogenesis, clinical features and histopathology of ameloblastoma.
2. Unicystic ameloblastoma.
3. Desmoplastic ameloblastoma.
4. Adenomatoid odontogenic tumour.
5. Squamous odontogenic tumour.
6. Discuss pathogenesis, clinical features and histopathology of calcifying epithelial odontogenic tumour.
7. Calcifications in calcifying epithelial odontogenic tumour.
8. Odontoma/complex odontoma/compound odontoma.
9. Ameloblastic carcinoma.

CHAPTER 5

Cysts of the oral and maxillofacial regions

Introduction of cyst

Kramer (1974) defined cyst as "a pathological cavity having fluid, semifluid or gaseous contents and which is not created by the accumulation of pus. It is frequently, but not always lined by epithelium" (Fig. 5.1).

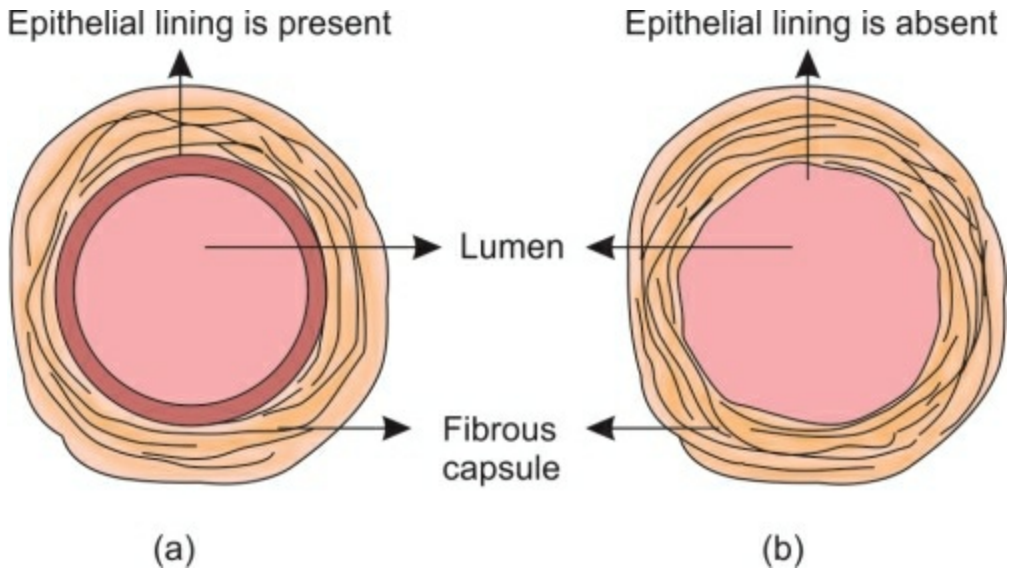
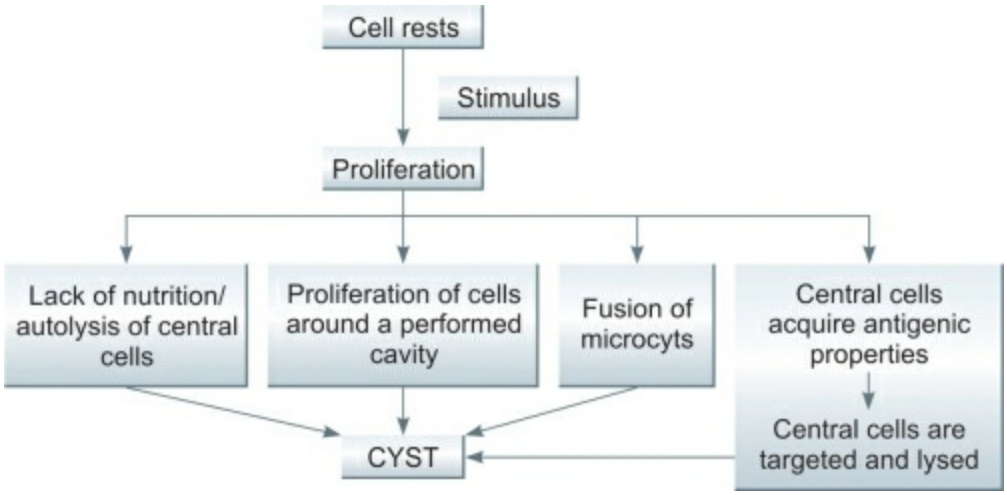


FIG. 5.1 Cyst: (a) *True cyst:* Cyst with epithelial lining; (b) *Pseudocyst:* Cyst without epithelial lining.

Cysts occur more commonly in jaw bones as compared to any other bones in skeletal system because of the embryology of facial bones and dental hard tissues.

Formation of cyst

Formation of cyst is depicted in Flowchart 5.1.



FLOWCHART 5.1 Formation of cyst.

Features of jaw cysts

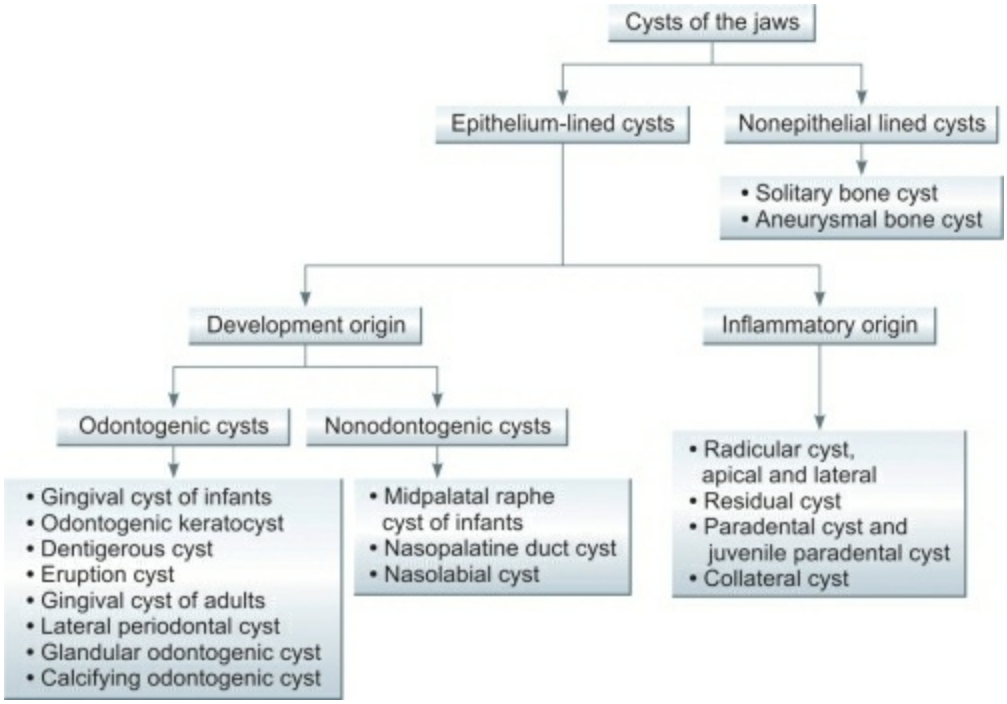
- Grow slowly, displacing rather than resorbing teeth.
- Symptomless, unless infected and frequently show radiographic findings.
- Form compressible and fluctuant swellings, if bone is perforated.
- Appear bluish, when close to the mucosal surface.
- Rarely large enough to cause pathological fracture.
- Form sharply defined radiolucencies with smooth borders.
- Fluid may be aspirated and thin-walled cysts may be transilluminated.

Classification of odontogenic cysts of the oral and maxillofacial regions

Shear in 2007 classified cyst of the oral and maxillofacial regions as given below.

- **Cysts of the jaw.** Classification of cyst of the jaw is given in Flowchart 5.2.
- **Cysts associated with the maxillary antrum**
 - Mucocele
 - Retention cyst
 - Pseudocyst
 - Postoperative maxillary cyst
- **Cysts of the soft tissues of the mouth, face and neck**
 - Dermoid and epidermoid cysts
 - Lymphoepithelial (branchial) cyst
 - Thyroglossal duct cyst

- Anterior median lingual cyst (intralingual cyst of foregut origin)
- Oral cysts with gastric or intestinal epithelium (oral alimentary tract cyst)
- Cystic hygroma
- Nasopharyngeal cyst
- Thymic cyst
- Cysts of the salivary glands—mucous extravasation cyst, mucous retention cyst, ranula and polycystic (dysgenetic) disease of the parotid
- Parasitic cysts—hydatid cyst, *cysticercus cellulosae* and trichinosis.



FLOWCHART 5.2 Cysts of the jaw—classification.

Frequency of odontogenic cysts occurrence (Jones et al, 2006)

- Radicular cyst
- Dentigerous cyst
- Odontogenic keratocyst
- Residual cyst
- Paradental cyst
- Lateral periodontal cyst
- Calcifying odontogenic cyst
- Gingival cyst

- Eruption cyst
- Glandular odontogenic cyst
- Epstein pearl

Odontogenic keratocyst (OKC)

(Synonym: Primordial cyst)

- The *1972 WHO classification* called it a *primordial cyst.*
- The *1992 WHO classification* called it an *odontogenic keratocyst (OKC).*
- The *2005 WHO classification* called it as:
 - *Keratocystic odontogenic tumour (KCOT):* Parakeratinized variant of OKC (more aggressive nature and high recurrence rate).
 - *Orthokeratinized odontogenic cyst (OOC):* Orthokeratinized variant of OKC (less aggressive nature and low recurrence rate).

Definition

Keratocystic odontogenic tumour is a benign intraosseous tumour of odontogenic origin with a characteristic lining of parakeratinized stratified squamous epithelium and potential aggressive, infiltrative behaviour. It may be solitary or multiple. The latter is usually one of the stigmata of the inherited naevoid basal cell carcinoma syndrome (NBCCS) *(WHO, 2005)*.

Variants of OKC (Main, 1970)

Depending on radiographic appearance, it has following variants (Fig. 5.2):

- *Envelopmental variant:* Cysts that embrace unerupted tooth.
- *Replacement variant:* Cysts that form in the place of a normal tooth.
- *Extraneous variant:* Cysts occur in the ascending ramus of mandible and away from the tooth.
- *Collateral variant:* Cysts occur adjacent to the roots of teeth.

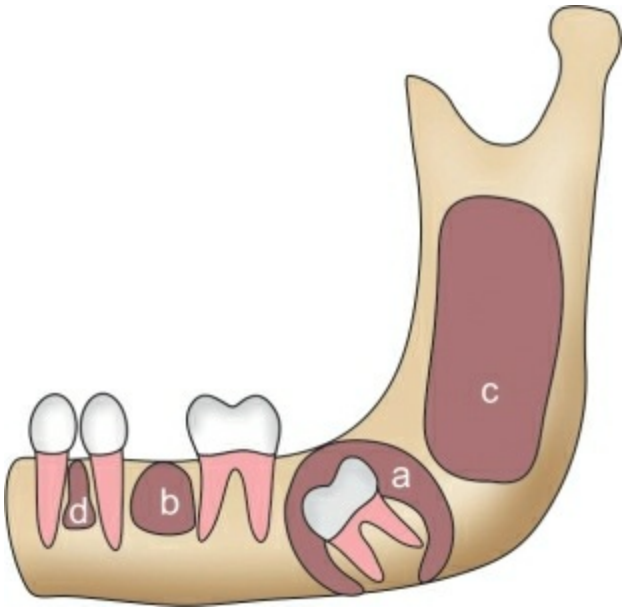


FIG. 5.2 Variants of OKC: (a) Envelopmental; (b) replacement; (c) extraneous; (d) collateral.

Pathogenesis

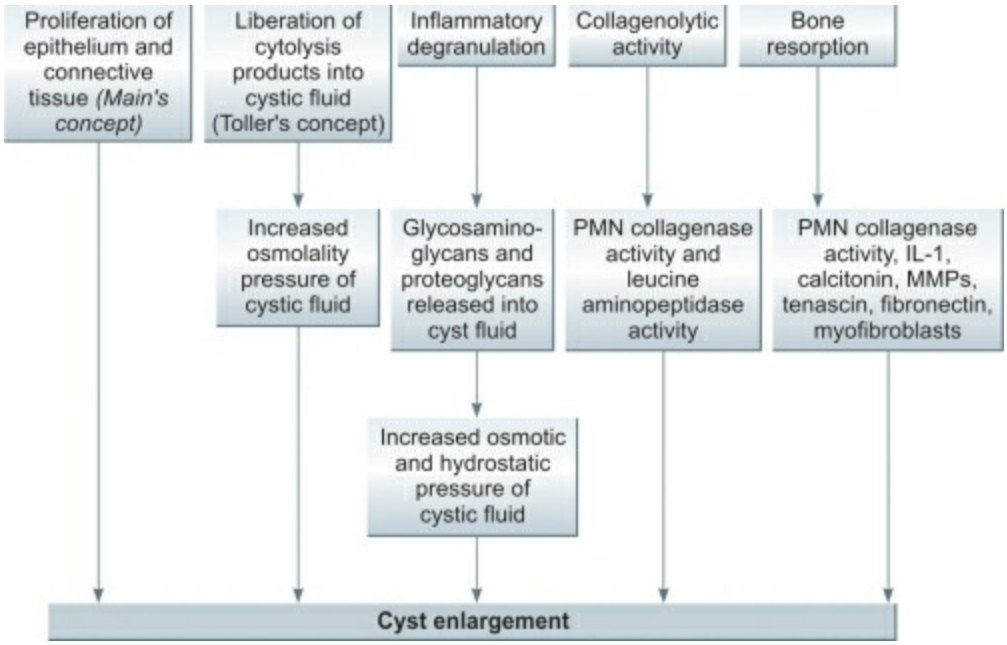
The sources of epithelium for cyst formation are:

- Cell rests of Serre: *Envelopmental variant* of OKC.
- Degeneration of stellate reticulum in enamel organ: *Replacement variant* of OKC.
- Epithelial off-shoots (hamartias) of the oral epithelium from basal layer: *Extraneous variant* of OKC.
- Epithelial rests of Malassez: *Collateral variant* of OKC.

Multiple OKCs are usually seen in patients with NBCCS. The cysts may arise directly from dental lamina in different sites. The stimulus for this phenomenon is not known, but the NBCCS is transmitted genetically as an autosomal dominant disorder.

Enlargement of cyst

The process of enlargement of cyst is depicted in Flowchart 5.3.



FLOWCHART 5.3 Enlargement of cyst.

Clinical features

It occurs in two forms:

1. Central/intraosseous variant
2. Peripheral/extraosseous variant

- **Age.** 20–40 years, 50–70 years (bimodal age distribution).
- **Gender.** Male predilection.
- **Location.** Posterior region of the mandible.
- **Signs and symptoms**
 - Patients are remarkably free of symptoms until the cyst reaches larger size.
 - Pain, mobility of the teeth and paraesthesia of the lower lip are frequently seen.
 - The clinically observable expansion of the bone occurs late in OKC because *it tends to extend in the medullary cavity of bone.*
 - In maxilla, the large sized lesions may lead to displacement and destruction of orbital floor and proptosis of the eyeballs.
 - Discharge of pus may be seen due to secondary infection.
 - *Peripheral odontogenic keratocyst* occurs on gingiva with clinical features similar to gingival cyst of adults and the histological features of a typical OKC.
 - Multiple OKCs in the jaws are seen in some cases, frequently they are

associated with NBCCS *(also called as Gorlin–Goltz syndrome or the Gorlin syndrome*).

The syndrome is inherited as a set of autosomal dominant characteristics with strong penetrance and variable expressivity. The clinical features of NBCCS include *multiple naevoid basal cell carcinomas and OKCs, bifid ribs, ectopic calcifications, plantar and palmar pits, central nervous system and ocular lesions, frontal bossing, ocular hypertelorism and other congenital skeletal defects*. The *NBCCS* gene is mapped to chromosome 9q22.3. In some cases, multiple OKCs may occur without the other overt features of the syndrome.

Radiographic features

- It shows well-defined unilocular or multilocular radiolucency (2.5:1) with smooth (slow-growing lesions) or scalloped margins.
- Some of the unilocular lesions have scalloped margins and these may be misinterpreted as multilocular lesions (scalloped margins suggest unequal growth activity in different parts of the cyst lining).
- The mandibular lesions enlarge and extend to the other side of the bone by crossing the midline. This is an important characteristic feature of OKC.
- Tooth displacement is commonly seen rather than root resorption.
- Radiographic variants of OKC (*mentioned earlier on page 156).*
- Peripheral odontogenic keratocyst shows saucerization of underlying bone.

Histopathology (fig. 5.3)

- The cysts are lined by a parakeratotic or orthokeratotic stratified squamous epithelium, which is usually about 5–8 cell layers thickness without rete ridges.
- Basal layer consists of palisaded cuboidal or columnar cells with reversal of polarity, whereas suprabasal layer composed of closely packed polyhedral cells.
- The parakeratotic epithelium may often show corrugated surface, which could be due to unequal growth pattern of the lining at various areas.
- In foldings of epithelial lining into the capsule with resultant inlets of the lumen or crypts may be due to active proliferation of epithelium into the capsule.
- The attachment between epithelium and the connective tissue capsule tends to be weak, which may cause separation in many areas.

- Sometimes, satellite cysts or proliferating epithelial islands are seen in the capsule.
- The cyst lumen contains desquamated keratin.
- The presence of an intense inflammatory infiltrate in fibrous capsule may cause loss of keratinization, thickening, development of rete ridges or ulceration of overlying epithelium.

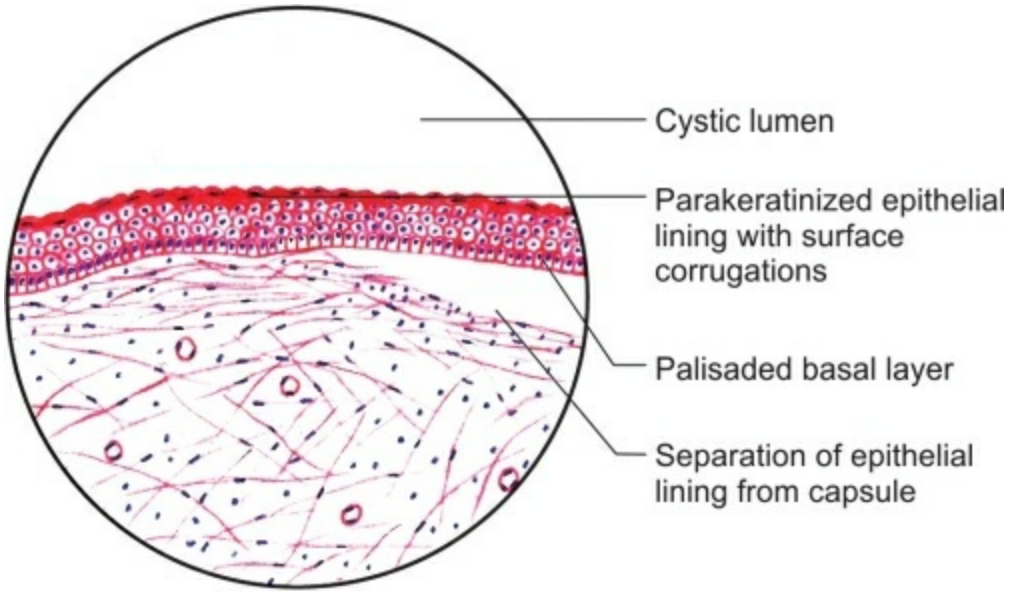


FIG. 5.3 Odontogenic keratocyst.

Differential diagnosis

- Ameloblastoma
- Dentigerous cyst
- Aneurysmal bone cyst

Prognosis and predictive factors

- OKC is the most common recurring lesion than any other cysts of the jaws.
- KCOT is a more aggressive lesion with high recurrence rate compared to OOC.
- Recurrences are more frequent in NBCCS patients than cysts in nonsyndrome patients.
- OKCs enucleated in one piece recur significantly less often than cysts enucleated in several pieces.

- Multilocular lesions recur more often than unilocular lesions.
- Cysts treated with enucleation or marsupialization will have high recurrence rate than surgical resection.
- Recurrent lesions may develop from epithelial off-shoots (hamartias) of the basal layer of the oral epithelium. So, overlying surface epithelium should be excised with the parent cyst.

Dentigerous cyst

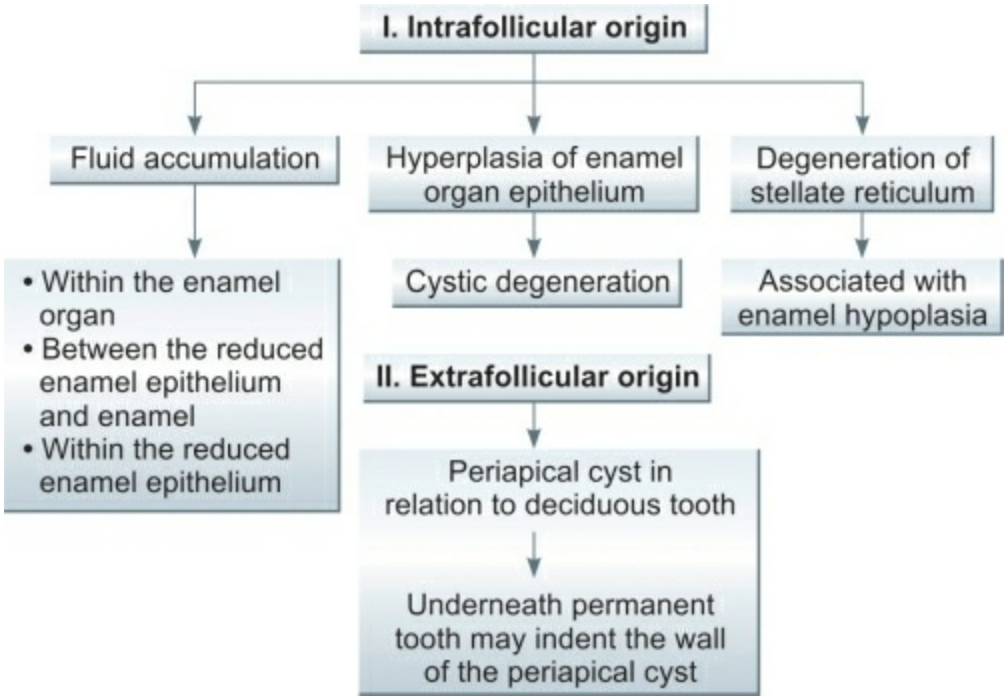
(Synonym: Follicular cyst)

Definition

Dentigerous cyst is defined as a cyst that originates by the separation of the dental follicle from the crown of an unerupted tooth *(dentigerous* means *tooth bearing).*

Pathogenesis

Pathogenesis of dentigerous cyst is given in Flowchart 5.4.



FLOWCHART 5.4 Pathogenesis of dentigerous cyst.

Clinical features

- **Age.** 20–40 years.
- **Gender.** Male predilection.
- **Site.** Mandibular third molar region.
- **Signs and symptoms**
 - It is an asymptomatic lesion (small-sized lesions) commonly associated with unerupted tooth.
 - Slow growing, painless swelling with cortical plates expansion is seen (large-sized lesions).
 - On palpation, thinning of cortical plates—*crepitus-like sensation.*
 - If the overlying bone is perforated—*fluctuation.*
 - Most of the lesions are detected during routine radiographic examination due to missing or impacted tooth.
 - Sometimes pain may be present due to secondary infection.
 - Paraesthesia on the affected part and pathological fractures of the jaw may occur.

Radiographic features

- Usually, well-defined unilocular radiolucency associated with unerupted tooth is seen.
- Occasionally, multilocularity is seen due to bony trabeculations.

Three radiographic variants are observed (Fig. 5.4):

a. *Central type:* The cyst envelops the crown symmetrically.
b. *Lateral type:* The cyst envelops the crown laterally and commonly associated with partially impacted tooth.
c. *Circumferential type:* The cyst envelops the entire tooth.

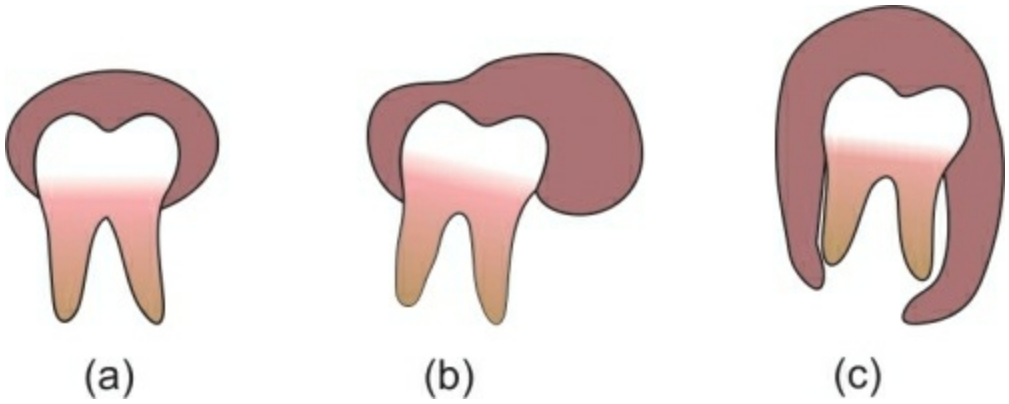


FIG. 5.4 Schematic diagram illustrating the manner in which the dental follicle expands to produce the radiographic appearances of: (a) central; (b) lateral; and (c) circumferential variants of dentigerous cysts.

Histopathology (fig. 5.5)

- It consists of nonkeratinized epithelial lining with 2–4 layers of flat or cuboidal cells.
- The connective tissue capsule is loosely arranged and contains considerable amount of glycosaminoglycan ground substance.
- Nests, islands and strands of odontogenic epithelium are often seen in the connective tissue capsule.
- Often, mucus-producing cells are seen in epithelial lining (*prosoplasia meaning forward* differentiation). The frequency of mucous cells is increased in proportion to the age of the patients.
- The intense inflammatory cell infiltrate in the capsule causes localized hyperplasia or discontinuity of overlying epithelium.
- Occasionally, bud-like thickenings of the epithelium into the fibrous capsule may be seen even in the absence of inflammation (*mural proliferations*).

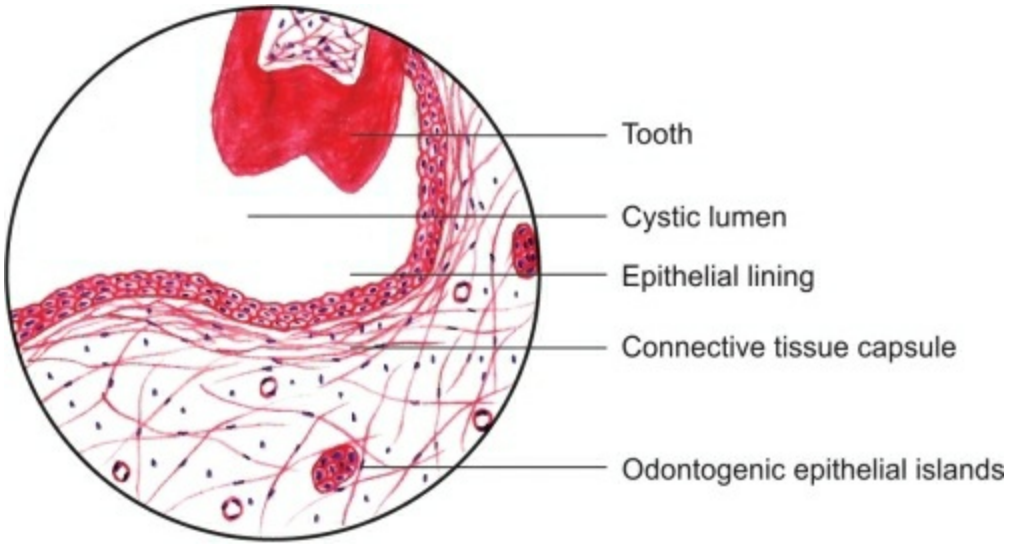


FIG. 5.5 Dentigerous cyst.

Complications of dentigerous cyst

- *Ameloblastoma:* It develops either from epithelial lining or from nests of odontogenic epithelium in the wall of the cyst.
- *Squamous cell carcinoma:* It develops from same two sources as described above.
- *Mucoepidermoid carcinoma:* It develops from epithelial lining containing mucous cells or cells with this potential transformation.

Differential diagnosis

- Adenomatoid odontogenic tumour
- Ameloblastoma (unicystic)
- Odontogenic keratocyst

Prognosis and predictive factors

- Smaller lesions—enucleation.
- Larger lesions—marsupialization or surgical resection.
- Recurrence is relatively uncommon.

Eruption cyst

(Synonym: Eruption haematoma)

Definition

Eruption cyst is defined as an odontogenic cyst with the histologic features of a dentigerous cyst that surrounds a tooth crown that has eruption through bone but not soft tissue and is clinically visible as a soft fluctuant mass on the alveolar ridges.

Pathogenesis

- It is similar to that of the dentigerous cyst, but the tooth in the case of the eruption cyst is impeded in the soft tissues of the gingiva rather than in the bone.
- Few studies reported that the administration of *cyclosporine* may lead to the development of eruption cysts.

Clinical features

- **Age.** 10–20 years.
- **Gender.** Male predilection.
- **Location.** Deciduous mandibular central incisors and permanent first molars region.
- **Signs and symptoms**
 - Usually bilateral, symmetrical and concurrent smooth swellings.
 - Over the erupting tooth, it may be either the colour of normal gingiva or blue hue.
 - It is usually painless unless infected and is soft and fluctuant.
 - Usually, surface trauma may result in a considerable amount of blood in the cystic fluid, which imparts a blue to purple-brown colour—*eruption haematoma*.
 - Transillumination is a useful diagnostic aid.

Radiographic feature

The cyst may show a soft tissue shadow, but there will be no bone involvement.

Histopathology

- The superficial aspect is covered by the parakeratinized stratified squamous epithelium (gingiva).
- Superficial epithelium is separated from the cyst by a strip of dense connective tissue of varying thickness which usually shows a mild chronic inflammatory cell infiltrate.

- The gingival connective tissue is acellular, densely collagenous and shows eosinophilic hue.
- The follicular connective tissue capsule is densely cellular, less collagenous and shows basophilic hue (due to high content of sulphated glycosaminoglycans in the ground substance).
- In noninflamed areas, the cystic epithelial lining shows 2–4 cell layers of flat or cuboidal cells, whereas in inflamed areas, epithelial lining shows hyperplasia and may form characteristic arcades.

Differential diagnosis

- Gingival cyst
- Dentigerous cyst
- Residual cyst

Prognosis and predictive factors

Treatment may not be required because the cyst usually ruptures spontaneously, permitting tooth to erupt. If not, simple surgical excision of the cyst is needed.

Gingival cyst of infants/midpalatal raphe cyst of infants

(Synonym: Dental lamina cyst of newborn)

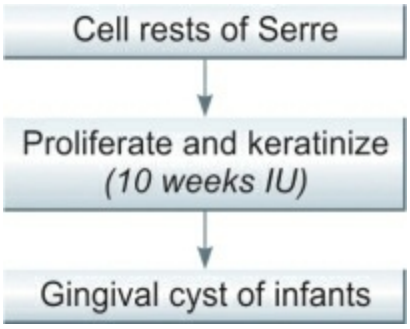
Definition

Gingival cyst of infants is small, superficial, keratin-filled cyst that is found on the alveolar mucosa of infants and resolves without treatment.

Note: The gingival and the midpalatal raphe cysts of infants are conveniently discussed together because they have similar clinical features, although the former lesion is of odontogenic origin and the latter lesion is a developmental origin.

Pathogenesis

- **Gingival cysts of infants**



- Gingival cysts may open on to the oral surface leaving clefts (or)
- It may interfere in tooth development (or)
- Some cysts may degenerate and disappear—the keratin and debris being digested by giant cells.

- **Midpalatal raphe cyst of infants**
 - Abortive glandular differentiation leading to cyst formation—Bohn's nodules.
 - Epithelial inclusions at the line of palatine shelves fusion—Epstein's pearls.

Clinical features

- **Age.** Infants.
- **Gender.** Female predilection.
- **Location.** Maxillary alveolus region.
- **Signs and symptoms**
 - The lesions are usually multiple, small, asymptomatic whitish or cream-coloured papules on the mucosa overlying the alveolar processes of neonates.
 - The cysts are round or ovoid in shape and may have a smooth or an undulating outline measuring about 2–3 mm in diameter.
 - Most of them undergo involution and disappear or rupture through the surface epithelium and exfoliate.
 - *Bohn's nodules or Epstein's pearls*
 - Bohn's nodules are scattered over the hard palate, often near the soft palate junction.
 - Epstein's pearls occur along the mid-palatine raphe of the hard palate.

Note: Cysts are absent in the soft palate due to consolidation of the soft

palate, and uvula takes place not by fusion instead by sub-epithelial mesenchymal merging of bilateral primordia.

Radiographic features

The cyst may show soft-tissue shadow or saucerization (superficial erosion) of the underlying bone.

Histopathology

- Cystic cavity fills keratin, usually in concentric laminations.
- A thin parakeratotic stratified squamous epithelial lining with flat basal cells is seen.
- Epithelial-lined clefts may develop between the cyst and surface oral epithelium.
- Sometimes, oral epithelium may be atrophic due to cystic pressure.
- *Midpalatine raphe cysts* show similar histological appearance as described above.

Differential diagnosis

- Eruption cyst
- Epulis (congenital)

Prognosis and predictive factors

- Treatment may not be required because the cyst usually ruptures spontaneously upon resultant contact with the oral mucosal surface.
- The lesions are rarely seen after 3 months of age.

Lateral periodontal cyst

(Synonym: Botryoid odontogenic cyst)

Definition

It is a slow-growing, nonexpansile developmental odontogenic cyst derived from one or more rests of the dental lamina, comprising of embryogenic lining of one to three cuboidal cells and distinctive focal thickenings (plaque).

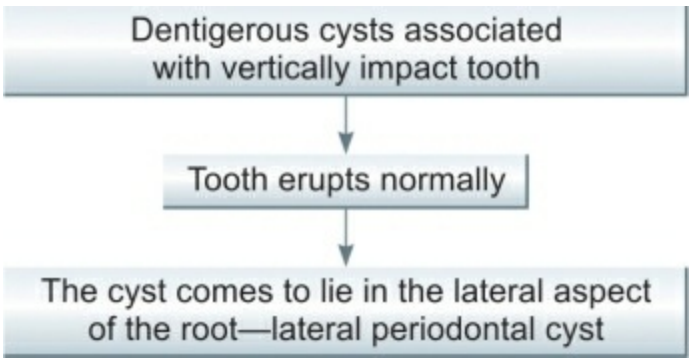
The multicystic variant of lateral periodontal cyst is known as *botryoid*

odontogenic cyst.

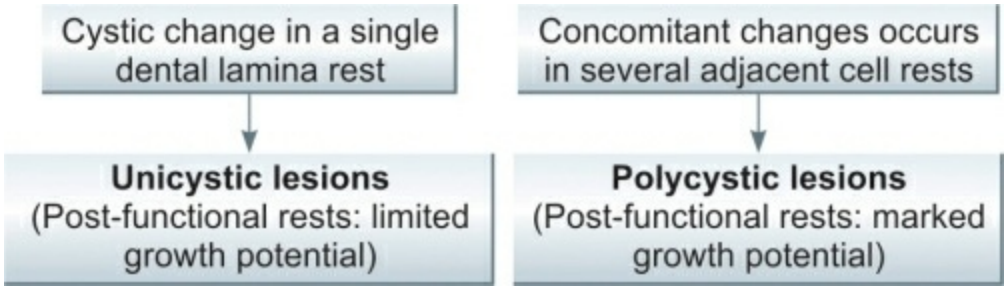
Pathogenesis

The possible sources of cyst formation are as follows:

- **Reduced enamel epithelium**



- **Remnants of dental lamina**



- **Cell rest of Malassez:** It is present in the periodontium and its position is conducive.

Clinical features

- **Age.** 21–81 years.
- **Gender.** No sex predilection.
- **Location.** Mandibular premolar area.
- **Signs and symptoms**
 - It is an asymptomatic lesion associated with vital tooth that may be usually detected during routine radiographic examination.
 - Usually, it occurs on facial aspect of gingiva, which appears normal or

bluish in colour.

- In some cases, pain may be present or may elicit tenderness on palpation.
- On palpation, some swellings may depict as *springy with eggshell crackling* (thinning of cortical plate) or *gelatinous feel* (cortical plate perforation).

Radiographic features

- Usually, it appears as a well-circumscribed, unilocular, round or oval-shaped radiolucent lesion on lateral aspect of the root.
- Most of the lesions are less than 1 cm in diameter except the botryoid variant, which is a larger and multilocular lesion extend up to or beyond periapical region also.

Histopathology

- Epithelial lining shows one to five layers of thickness of squamous or cuboidal cells.
- Abundant glycogen-rich clear cells are frequently seen in the epithelial lining.
- Usually, it shows *localized plaques or thickenings* of the epithelial lining extending into surrounding capsule. It may also produce mural bulges protruding into lumen.
- The epithelium–connective tissue interface will be tenacious and may peel off easily.
- Small epithelial nests or follicles are seen in the fibrous capsule. These nests may enlarge and be the source for multiple microcysts formation —*botryoid odontogenic cyst (botryoid* means cluster of grapes).
- Few cysts are lined by hyperplastic stratified squamous epithelium with verrucous projections and shedding keratin into the lumen—*verrucous odontogenic cyst.*

Differential diagnosis

- Gingival cyst of adults
- Radicular cyst
- Lateral periodontal abscess

Prognosis and predictive factors

- Conservative enucleation without damage to the adjacent teeth is recommended.
- Recurrence is unusual, although it has been reported with the botryoid variant, presumably because of its polycystic nature.

Gingival cyst of adults

Definition

- A small developmental odontogenic cyst of the gingival soft tissue derived from the rests of the dental lamina, containing a lining of embryonic epithelium of cuboidal cells and distinctive focal thickenings similar to the lateral periodontal cyst.

Gingival cyst of adults represents the extraosseous counterpart of the intraosseous lateral periodontal cyst.

Pathogenesis (fig. 5.6)

- The possible sources of cyst formation are as follows:
 - Remnants of odontogenic epithelium
 - Traumatic implantation of surface epithelium
 - Cystic degeneration of deep projections of gingival epithelium
 - Heterotopic glandular elements
- The gingival cyst of adults and the lateral periodontal cyst may arise from the same source. *Buchner and Hansen (1979)* postulated that the lateral periodontal cyst is formed from the reduced enamel epithelium by dilatation of the follicle *before eruption* of the tooth, whereas the gingival cyst of adults is derived from reduced enamel epithelium *after eruption* of the tooth.
- Origin of these cysts from *post-functional epithelium* (reduced enamel epithelium) would help to explain the unaggressive nature of the gingival cyst of adults and the lateral periodontal cyst.

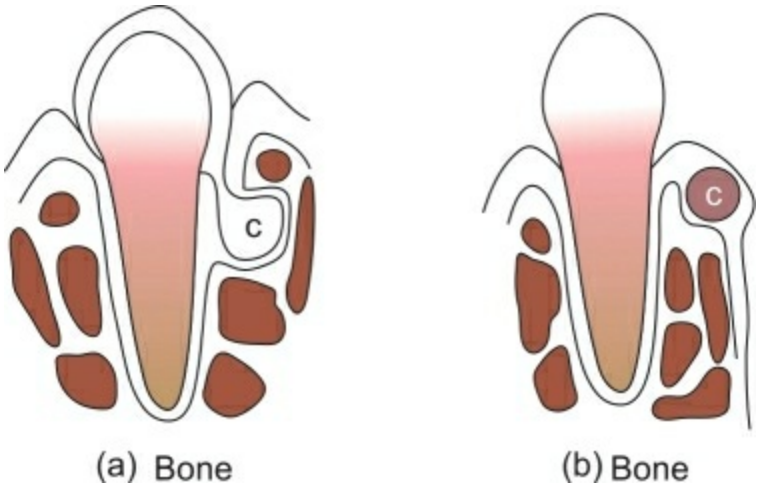


FIG. 5.6 Schematic diagram illustrating the pathogenesis of lateral periodontal cyst (a); and gingival cyst of adults (b). (c—cyst).

Clinical features

- **Age.** 23–70 years.
- **Gender.** Female predilection.
- **Location.** Premolar–canine region of the mandible.
- **Signs and symptoms**
 - It occurs as a soft, well-circumscribed, round to oval-shaped, slow-growing, painless swelling and usually occurs on facial aspect of attached gingiva or interdental papilla.
 - The adjacent teeth will be vital.
 - Usually, it shows normal or bluish in colour.

Radiographic features

- Usually, no radiographic changes are seen.
- Sometimes saucerization of the underlying bone may be seen.

Histopathology

- Epithelial lining may be:
 - Thin, composed of 1–3 layers of flat to cuboidal cells (or)
 - Thick, stratified, squamous epithelium without rete ridges. Sometimes numerous clear cells are seen (or)
 - Atrophic and only ghost-like outline remains.
- The epithelium–connective tissue interface is tenuous and can be peeled off in many areas.

- The fibrous capsule is usually uninflamed except in the region close to the junctional epithelium, where a dense chronic inflammatory infiltrate may be seen.
- Layers of keratin may be present in the cystic lumen.

Differential diagnosis

- Lateral periodontal cyst
- Pyogenic granuloma
- Radicular cyst

Prognosis and predictive factors

- Surgical excision.
- Prognosis is excellent.

Glandular odontogenic cyst

(Synonym: Sialo-odontogenic cyst)

Definition

Glandular odontogenic cyst (GOC) is a large unilocular or multilocular odontogenic cyst probably derived from the rests of dental lamina, consisting of a stratified squamous epithelial lining with numerous mucus-secreting cells.

Pathogenesis

- This cyst may arise from the remnants of dental lamina, which are capable of glandular differentiation.
- It may be a variant of lateral periodontal cyst.

Clinical features

- **Age.** 31–81 years.
- **Gender.** Male predilection.
- **Location.** Canine to molar region of mandible.
- **Signs and symptoms**
 - Usually, it appears as a painless swelling of the jaw, unless it is secondarily infected.
 - Maxilla lesions show facial and nasal swelling with infraorbital

paraesthesia.

- GOC is an aggressive or potentially aggressive cystic lesion that usually has a history of recurrence (if not adequately excised).

Radiographic features

- It appears as a well-defined multilocular or unilocular radiolucency with sclerotic border.
- Cortical plate may show thinning, perforation or erosion.
- Root resorption and tooth displacement are seen in few cases.

Histopathology (fig. 5.7)

- The cyst will be lined by a nonkeratinized (and/or ciliated) stratified squamous epithelium of variable thickness with a chronic inflammatory infiltration in the connective tissue capsule.
- Characteristically, the superficial layer of the epithelial lining consists of columnar or cuboidal cells—*hobnail appearance*.
- Epithelial lining may show numerous goblet cells, glandular or pseudoglandular structures with intraepithelial crypts or microcysts or pools of eosinophilic material.
- Epithelial thickenings or plaques may be seen in some lesions. These plaques are identical to those in the lateral periodontal cyst and may either protrude into the cyst cavity or extend into the connective tissue capsule.

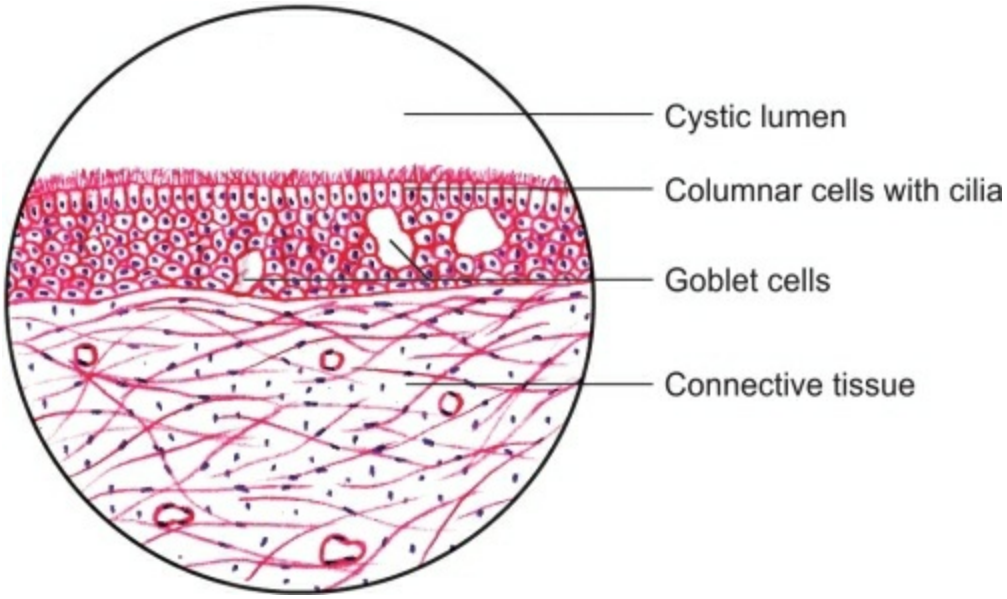


FIG. 5.7 Glandular odontogenic cyst.

Differential diagnosis

- Lateral periodontal cyst
- Odontogenic keratocyst
- Ameloblastoma

Prognosis and predictive factors

- Usually, enucleation or curettage is done; however, this cyst shows a propensity for recurrence.
- Due to its aggressive nature and tendency to recur, en bloc resection is recommended, particularly for multilocular lesions.

Calcifying odontogenic cyst

(Synonyms: Gorlin cyst; calcifying ghost cell odontogenic cyst)
The calcifying odontogenic cyst (COC) was first described by *Gorlin (1962)*, hence the eponym *Gorlin cyst.*

Definition

A cystic lesion in which the epithelial lining shows a well-defined basal layer of columnar cells, an overlying layer that is often many cells thick and that may resemble stellate reticulum, and masses of *ghost* epithelial cell that may be in the epithelial lining or in the fibrous capsule. The *ghost* epithelial cells

may become calcified. Dysplastic dentine may be laid down adjacent to the basal layer of the epithelium, and in some instances, the cyst is associated with an area of more extensive dental hard tissue formation resembling that of a complex or compound odontoma *(WHO, 2005).*

Classification

Based on the biological behaviour, *Praetorius (2006)* classified COC into three groups—*cysts, benign tumours and malignant tumours.*

The term 'COC' should be used specifically to designate the isolated unicystic lesions without any associated tumours or hamartomas.

Group 1: Simple cyst—calcifying odontogenic cyst

Group 2: Cysts associated with odontogenic hamartomas or benign neoplasms—calcifying cystic odontogenic tumours (CCOT). The following combinations have been published:

- CCOT associated with an odontoma
- CCOT associated with adenomatoid odontogenic tumour
- CCOT associated with ameloblastoma
- CCOT associated with ameloblastic fibroma
- CCOT associated with ameloblastic fibro-odontoma
- CCOT associated with odontoameloblastoma
- CCOT associated with odontogenic myxofibroma

Group 3: Solid benign odontogenic neoplasms with similar cell morphology to that in the COC with dentinoid formation—dentinogenic ghost cell tumour.

Group 4: Malignant odontogenic neoplasms with features similar to those of the dentinogenic ghost cell tumour—ghost cell odontogenic carcinoma.

Pathogenesis

- COC may arise as a *de novo* lesion.
- It may develop from reduced enamel epithelium or remnants of odontogenic epithelium in the follicle, gingival tissue or bone.
- COC may develop as a secondary phenomenon in pre-existing odontogenic tumours.
- Praetorius (1981) believes that the dentinogenic ghost cell tumour is a de novo neoplasm, but the COC plus benign neoplasm or hamartoma is a cyst from the beginning.

Clinical features

It occurs in two forms:
1. Central/intraosseous variant
2. Peripheral/extraosseous variant

- **Age.** 20–60 years.
- **Gender.** No sex predilection.
- **Location.** Canine to first molar region of both mandible and maxilla.
- **Signs and symptoms**
 - The intraosseous variant often presents as a painless slow-growing swelling, which may produce extensive bony hard expansion.
 - Occasionally, it may perforate the cortical plate and extend into overlying soft tissues.
 - In few cases, displacement of the teeth can be seen.
 - Extraosseous lesions tend to be pink to red in colour and appear as a circumscribed elevated mass on gingiva.

Radiographic features

- Intraosseous lesions show well-defined unilocular or multilocular radiolucent areas containing radiopaque masses of varying sizes *(snow-driven appearance).*
- Frequently, displacement of teeth and resorption of the roots are seen.
- The extraosseous lesions show saucerization of the underlying bone.

Histopathology (fig. 5.8)

- The epithelial lining shows palisaded basal layer consisting of columnar or cuboidal cells with hyperchromatic nuclei polarized away from the basement membrane. The suprabasal layer consists of stellate reticulum-like cells.
- The presence of *ghost cells* in the epithelial lying is the most characteristic feature.
- **Ghost cells**
 - These appear as well-defined eosinophilic masses and/or basophilic nuclear remnants in it.
 - The ghost cells may represent abnormal keratinization that have an affinity for calcification or the product of coagulative necrosis of odontogenic epithelium or dystrophic calcification or foreign body reaction with the formation of multinucleate giant cells.
 - The ghost cells may also occur in *craniopharyngioma, the calcifying epithelioma of Malherbe, dentinogenic ghost cell tumour* and *ghost cell*

odontogenic carcinoma.

- Often, subepithelial dentinoid material is seen.
- Budding from the basal layer of epithelial lying into the connective tissue capsule and epithelial proliferations into the lumen are frequently seen.
- Usually, fibrous capsule shows islands of odontogenic epithelium or satellite cysts.

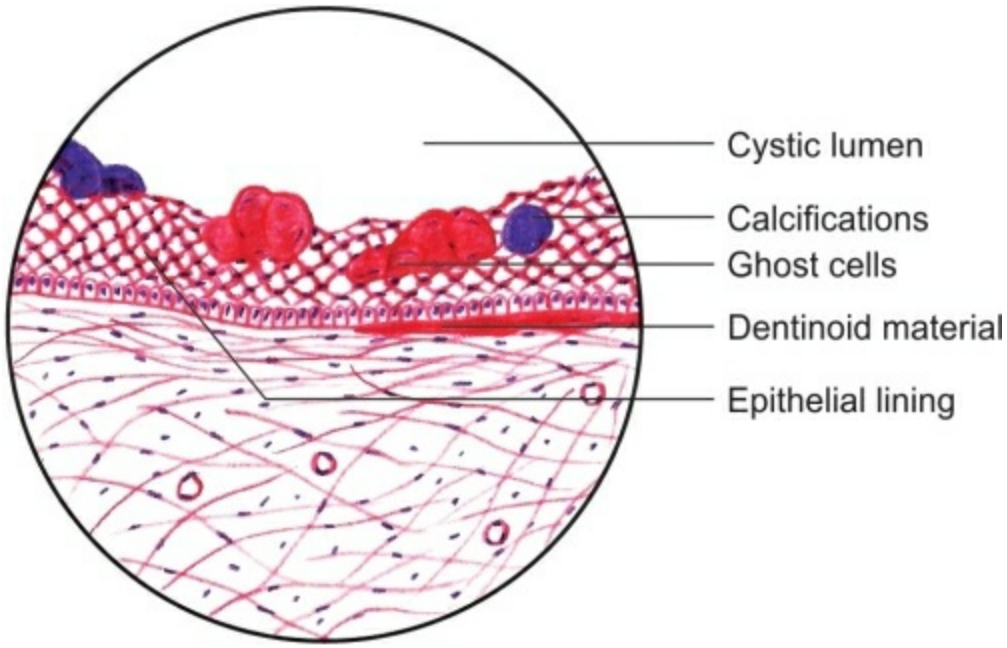


FIG. 5.8 Calcifying odontogenic cyst.

Differential diagnosis

- Calcifying epithelial odontogenic tumour
- Adenomatoid odontogenic tumour
- Ameloblastoma

Prognosis and predictive factors

- *Isolated COC:* Recurrence is less common and it can be treated by simple enucleation.
- *COC associated with tumour:* Recurrence is common and surgical resection is required.

Nasopalatine duct cyst

https://t.me/RoyalDentistryLibrary/

(Synonym: Incisive canal cyst)

Definition

Nasopalatine duct cyst is a relatively common nonodontogenic intraosseous, cystic lesion arising within the nasopalatine duct or the incisive canal.

Pathogenesis

- The exact mechanism is unknown.
- The nasopalatine duct cyst is derived from embryonic epithelial residues in the nasopalatine canal or epithelial cells included in the lines of fusion of embryonic facial processes. The latter view has been extremely controversial, as many embryologists and pathologists discount the possibility of such an origin, stating that the grooves between the processes are smoothed out by proliferation of the underlying mesenchymal growth centres (*merging*).
- The vomer–nasal organs of Jacobson are sometimes mentioned as a possible source of cysts in the incisive canal but this is most unlikely.

Clinical features

- **Age.** 30–60 years.
- **Gender.** Male predilection.
- **Location.** Anterior region of the mid palate.
- **Signs and symptoms**
 - The most common symptom is the swelling, which usually occurs in the anterior region of the mid palate or in the midline on the labial aspect of the alveolar ridge or in some cases, *through and through* fluctuation may be elicited between the labial and palatal swellings.
 - The swelling may be associated with pain (due to pressure on the nasopalatine nerves) or discharge. Sometimes discharge or pain will be the only symptom elicited. Various combinations of swelling, discharge and pain may also occur in few cases.
 - The discharge may be mucoid—salty taste or purulent—foul taste.
 - There may be a history of recurrent swellings that periodically discharge and then regresses.
 - The adjacent teeth will be vital.

Radiographic features

https://t.me/RoyalDentistryLibrary/

- Usually, it appears as *heart-shaped* radiolucent area between maxillary central incisors, this appearance is either because they notched by the nasal septum during their expansion or the nasal spine may superimpose on the radiolucent area or if there are bilateral cysts.
- The incisor roots may diverge, but root resorption is rare.
- The adjacent teeth shows intact lamina dura around the roots (indicates vital pulp).
- Sometimes, the cyst may be confused with the incisive foramen. In such cases, a second radiograph should be taken at a different angulation.

The average size of nasopalatine duct cyst is 1–2.5 cm in diameter, whereas incisive foramen will be 6 mm in diameter. Therefore, if the suspected lesion is measuring about 6 mm or less without clinical symptoms, the diagnosis should be incisive foramen rather than a cyst.

Histopathology

- The epithelial lining is extremely variable. Stratified squamous, pseudostratified ciliated columnar, cuboidal, columnar, or primitive flat epithelium may be seen, individually or in combination.
- Goblet cells may be found frequently in epithelial lining.
- Respiratory epithelium probably originates from nasopalatine duct adjacent to the nasal cavity, whereas those lined by stratified squamous epithelium may develop from the lower portion of the duct.
- A valuable diagnostic feature of nasopalatine duct cysts is the presence of nerves and blood vessels with small foci of mucous glands in the fibrous capsule.

Differential diagnosis

- Nasopalatine duct
- Reticular cyst
- Lateral periodontal cyst

Prognosis and predictive factors

- Surgical enucleation.
- Recurrence is rare.

Note: In recent years, the existence of *median palatine cyst, median alveolar*

https://t.me/RoyalDentistryLibrary/

cyst and globulomaxillary cyst as separate entities has been questioned and these were excluded from the 1992 WHO classification of jaw cysts. Previously, it had been thought that these cysts developed from epithelium entrapped in the process of fusion of embryonic processes, but now it is believed that these represent *posterior extension of an incisive canal cyst in the case of median palatine cystandanterior extension in the case of median alveolar cyst* and *odontogenic keratocyst in the case of the globulomaxillary cysts*. Sometimes, median alveolar cyst may also be a keratocyst derived from dental lamina in the midline of the maxilla.

Nasolabial cyst

(Synonyms: Nasoalveolar cyst; Klestadt cyst)

Definition

Nasolabial cyst is a rare developmental soft tissue cyst that occurs in the upper lip lateral to the midline deep into the nasolabial fold.

Pathogenesis

- It may arise from epithelium enclaved at the site of fusion of the globular, lateral nasal and maxillary processes. This concept, however, is not tenable as the embryological basis for it has been seriously disputed.
- It may also develop from the lower anterior part of the nasolacrimal duct.

Clinical features

- **Age.** 12–75 years.
- **Gender.** Female predilection.
- **Location.** It occurs outside the bone in the nasolabial folds below the alae nasi.
- **Signs and symptoms**
 - The most frequent symptom will be the swelling. Sometimes, the patients complained of pain and difficulty in nasal breathing, but pain and discharge is generally present among infected cysts.
 - The cysts grow slowly, producing a swelling of the lip and form a bulge in the labial sulcus. These fill out the nasolabial fold and often lift the alae nasi, distort the nostril and produce a swelling in the floor of the nose.

https://t.me/RoyalDentistryLibrary/

- The cysts are fluctuant and on bimanual palpation, fluctuation may be elicited between the swelling on the floor of the nose and labial sulcus.

Radiographic features

Radiolucent depression on the labial surface of the anterior maxilla can be detected in a tangential view (PA view) radiograph.

Histopathology

- Usually, the cyst is lined by nonciliated pseudostratified columnar epithelium, but in some cases, epithelial lining may consist of one to two layers of cuboidal or flat squamous cells.
- Numerous goblet cells are frequently seen in epithelial lining.
- The fibrous capsule is relatively acellular and is either loosely or densely collagenous.
- Mucous glands are commonly seen in the fibrous capsule.

Differential diagnosis

- Nasopalatine duct cyst
- Lateral periodontal cyst/abscess
- Gingival abscess

Prognosis and predictive factors

- Complete surgical excision of the cyst is recommended.
- Recurrence is rare.

Radicular cyst

(Synonyms: Periapical cyst; apical periodontal cyst)

Definition

- **Radicular cysts** are the most common inflammatory cysts and arise from the epithelial residues in the periodontal ligament as a result of periapical periodontitis following death and necrosis of the pulp (nonvital tooth).
- **Residual cyst** is a radicular cyst that is retained in the jaws after the removal of offending nonvital tooth.
- *Inflammatory periodontal cyst* or *inflammatory collateral cyst* is an inflammatory cyst that occurs towards the lateral aspect of a root as a

https://t.me/RoyalDentistryLibrary/

consequence of an inflammatory process in a periodontal pocket.

- *Paradental cyst* is an inflammatory cyst that occurs on the lateral aspects of the roots of partially erupted mandibular third molars with an associated history of pericoronitis.
- *Mandibular infected buccal cyst* is an inflammatory cyst that occurs on the buccal surfaces of the mandibular molars in young children.

Pathogenesis

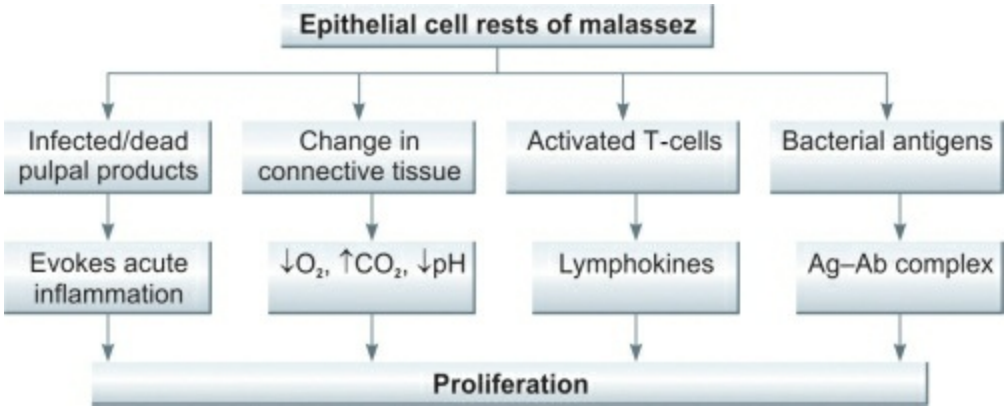
The formation of radicular cyst occurs in three phases:

1. Phase of initiation
2. Phase of cyst formation
3. Phase of cyst enlargement

Phase of initiation

The epithelial linings of these cysts are derived from the epithelial cell rests of Malassez in the periodontal ligament, which lie near periapical granuloma associated with nonvital teeth. The epithelial cell rests are initiated to proliferate as given in Flowchart 5.5.

Phase of cyst formation



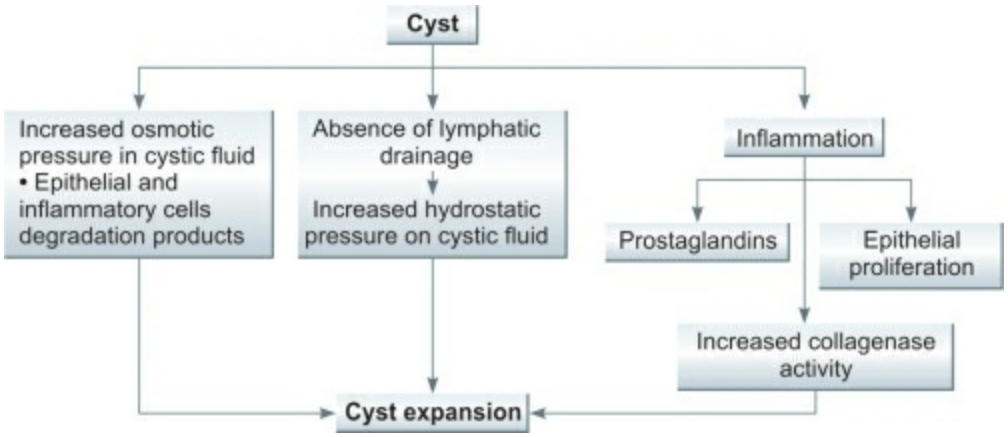
FLOWCHART 5.5 Phase of initiation.

The phase of cyst formation is described in Flowchart 5.1.

Phase of cyst enlargement

The phase of cyst enlargement is depicted in Flowchart 5.6.

https://t.me/RoyalDentistryLibrary/



FLOWCHART 5.6 Phase of cyst enlargement.

Clinical features

- **Age.** 40–50 years.
- **Gender.** No gender predilection.
- **Location.** Maxillary anterior region.
- **Signs and symptoms**
 - Usually, radicular cysts are asymptomatic and are discovered when periapical radiographs are taken due to tooth discolouration (nonvital tooth).
 - The bony hard, slow-growing swelling is often seen. As the cyst increases in size, the covering bone becomes very thin despite subperiosteal bone deposition, which exhibits *springiness* or *eggshell* crackling. If the cyst has completely eroded the bone, the lesion will be *fluctuant*.
 - Pain will be elicited due to secondary infection. Occasionally, a sinus may lead from the cyst cavity to the oral mucosa.
 - Involved tooth will be nonvital. Vitality test elicits negative response.
 - Radicular cysts occur rarely among deciduous teeth due to following reasons:
 - Pulpal and periapical infections in deciduous teeth tend to drain more readily than those of permanent teeth.
 - The antigenic stimuli that evoke the changes leading to the formation of radicular cysts may be different among deciduous teeth.
 - Pulpal floor of the deciduous teeth contains numerous accessory canals which intend to cause furcation involvement rather than periapical lesions.

https://t.me/RoyalDentistryLibrary/

Radiographic features

- Usually, the lesion measuring 10–14 mm is *granuloma*; the lesion measuring 15 mm or more is *cyst.*
- Classically, radicular cysts appear well-defined, round or ovoid-shaped radiolucency with a thin sclerotic border, which indicates a reaction of the bone to the slowly expanding lesion.
- In infected or rapidly enlarging cysts, the sclerotic border around the cysts may not be observed.
- Loss of continuity of lamina dura of the involved tooth is frequently seen.
- Root resorption may be seen in few lesions.

Histopathology (fig. 5.9)

- The cystic fluid contents are usually brown due to breakdown of blood and when cholesterol crystals are present they impart a shimmering gold or straw colour.
- Usually, these are lined by stratified squamous epithelium. These linings may be discontinuous in part and range in thickness from 1 to 50 cell layers.
- The nature of the lining may depend on the age or stage of development of the cyst or on the intensity of the inflammation. In early cysts, the epithelial lining may be proliferative and show arcading pattern with an intense inflammatory process but as the cyst enlarges, the lining becomes quiescent and fairly regular with a certain degree of differentiation to resemble a simple stratified squamous epithelium.
- *Rushton's hyaline bodies* are frequently found in the epithelial lining. These are linear, curved or hairpin-shaped structures and sometimes these are also concentrically laminated.
 Origin: These may be:
 - Secretory product of odontogenic epithelial cells.
 - Haematogenous origin—thrombi shrank centrifugally and underwent splitting, or they may calcify.
 - Degenerating red blood cells.
- The cholesterol crystals are usually deposited in the fibrous capsule. These behave as foreign bodies and excite a foreign body giant cell reaction. In histological sections, the cholesterol crystals are dissolved out and clefts surrounded by dense aggregations of multinucleate giant cells are seen. The main source of cholesterol crystals are:
 - Disintegrating red blood cells

https://t.me/RoyalDentistryLibrary/

- Degeneration and disintegration of lymphocytes and plasma cells
- β-Lipoproteins in the plasma pass through the fragile thin-walled blood vessels in the inflamed portions of cyst wall.

- Varying intensities of acute and chronic inflammatory cell infiltrate are present in connective tissue capsule.
- Calcifications are frequently present in a cyst of longer time.
- Simon (1980) showed two types of radicular cysts:
 1. **True radicular cyst** which contains a closed cavity entirely lined by epithelium.
 2. **Periapical pocket cyst (bay cyst)** in which the epithelium is attached to the margins of apical foramen in such a way that the cyst lumen is open to the affected root canal. Thus, it is expected that the pocket cyst would heal after treatment or tooth extraction, while the true cyst is self-sustaining and may persist even in the absence of aetiology.

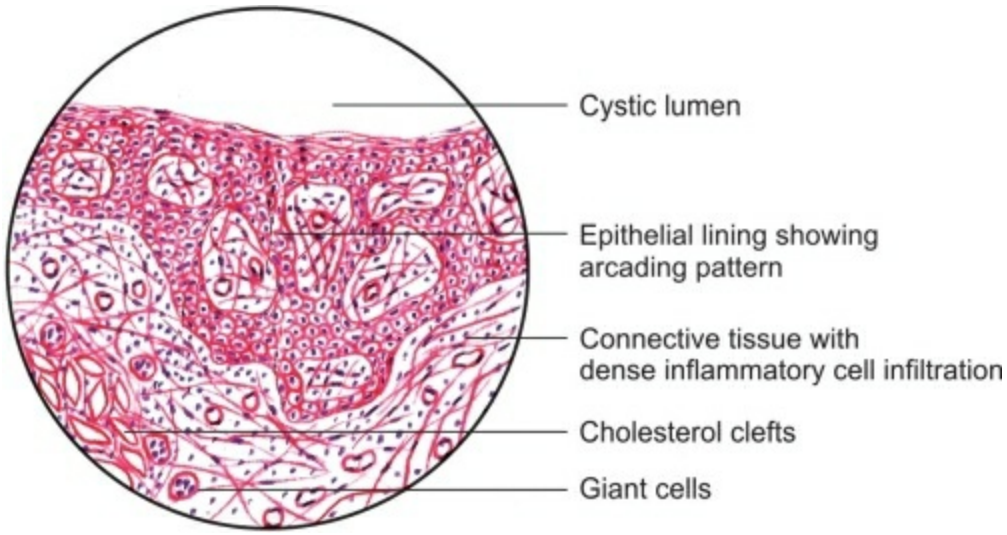


FIG. 5.9 Radicular cyst.

Differential diagnosis

- Periapical granuloma
- Central giant cell granuloma
- Periapical abscess

Prognosis and predictive factors

https://t.me/RoyalDentistryLibrary/

- Small cysts—root canal treatment of the affected teeth and apical curettage.
- Large cysts—surgical enucleation or marsupialization.

Residual cyst is the radicular cyst that is retained in the jaws after the removal of offending nonvital tooth. It may be asymptomatic or symptomatic:

- *Asymptomatic cysts:* These are usually seen in the mandibular premolar region and there is a direct relationship between the age of the cyst and the radiological and histological evidence of mineralization. There is an overall reduction in epithelial thickness with cyst age and all cysts show minimal chronic inflammatory changes. These residual cysts are slowly resolving lesions.
- *Symptomatic cysts:* These may produce pain or swelling or both. The mean cyst size is larger than that of asymptomatic cysts and has a negative correlation with cyst age. It occurs commonly in the mandibular premolar region. Cortication of the cyst wall is radiographically significant. Acute and chronic inflammatory cell infiltration shows in variable intensity.

Solitary bone cyst

(Synonyms: Traumatic bone cyst; haemorrhagic bone cyst; unicameral bone cyst)

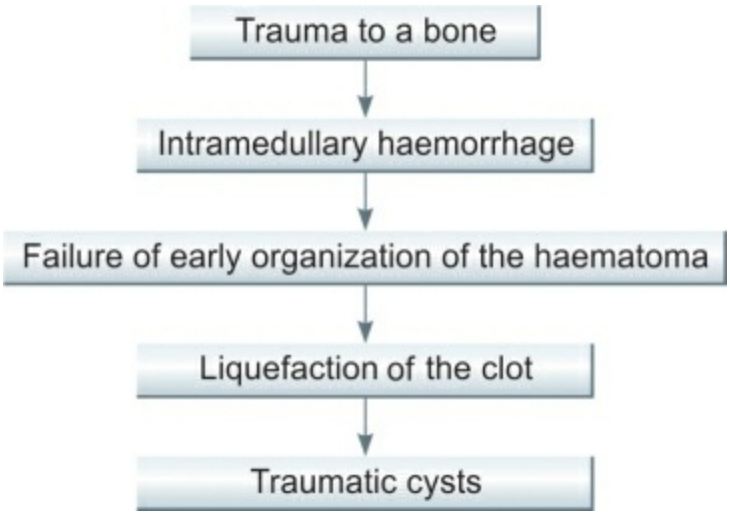
Definition

The simple bone cyst is an empty or fluid-containing cavity within the bone that is devoid of an epithelial lining.

Pathogenesis

- *Traumatic theory*

https://t.me/RoyalDentistryLibrary/



- Cystic degeneration of primary bone tumours.
- A result of faulty calcium metabolism such as parathyroid disease.
- Ischaemic necrosis of fatty bone marrow.
- The end result of a low-grade chronic infection.
- Unequal balance of osteoclasis and repair of bone due to trauma.

Clinical features

- **Age.** 10–60 years.
- **Gender.** No gender predilection.
- **Location.** Posterior region of the mandible.
- **Signs and symptoms**
 - Usually, asymptomatic lesion.
 - Swelling may be a presenting symptom. Sometimes patient may complain of labial paraesthesia.
 - Most of the patients give a history of significant trauma in the involved area.
 - All the related teeth will be vital.

Radiographic features

- It appears as a unilocular or multilocular radiolucent area with irregular but definite border and slight cortication.
- *Cone-shaped morphology*—one lateral margin of the lesion forms an angular interface with normal bone with two planes converging at a 45° angle to produce a sharp cone effect. Most often, the cone points anteriorly towards the midline.
- The lamina dura may or may not be lost and occasionally root resorption

https://t.me/RoyalDentistryLibrary/

is seen.

Histopathology

- On surgical exposure, the cyst cavity is found to be empty. In some cases, blood or serosanguineous or serous fluid may be present.
- The cyst will be lined by a thin band of fibrovascular connective tissue or demonstrate a thickened myxofibromatous proliferation that often intermixed with trabeculae of bone.
- Epithelial lining will be absent.
- Haemorrhage and haemosiderin pigments are usually present with scattered multinucleated giant cells.
- Long-standing cysts show more dense fibrous capsules.

Differential diagnosis

- Aneurysmal bone cyst
- Central giant cell granuloma
- Ameloblastoma

Prognosis and predictive factors

- The treatment is done by surgical exploration of the cyst, which helps in causing further haemorrhage in the area with subsequent healing.
- Some lesions may resolve spontaneously.

Aneurysmal bone cyst

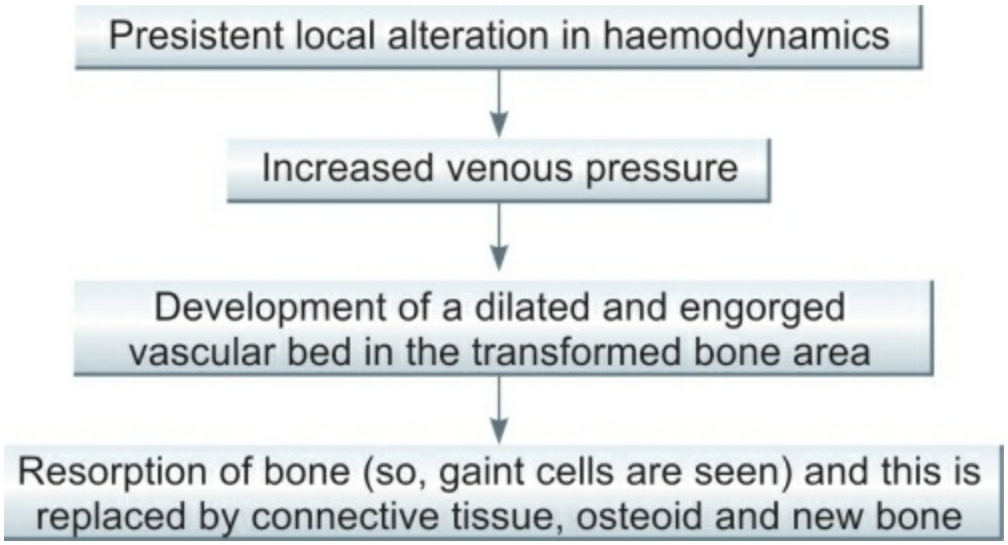
(Synonyms: Ossifying haematomas; osteitis fibrosa cystica)

Definition

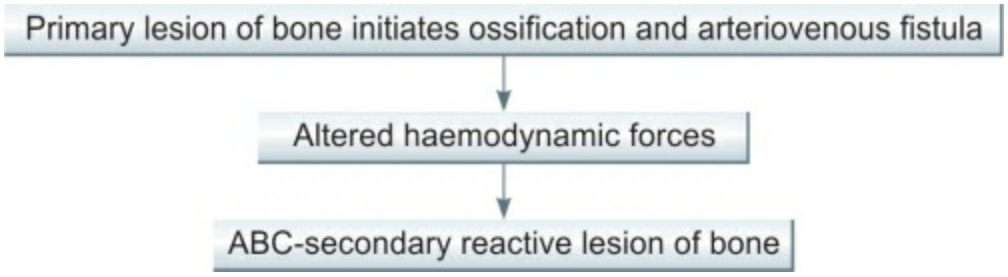
Aneurysmal bone cyst (ABC) is a benign intraosseous lesion characterized by blood-filled spaces of varying sizes associated with a fibroblastic tissue containing multinucleated giant cells, osteoid and woven bone (WHO, 2005).

Pathogenesis

- Lichtenstein (1942) proposed the following:



- Biesecker (1970) reported that aneurysmal bone cysts accompany with benign primary lesion of bone.



- Levy (1975) reported that ABC occurs secondary to or in association with osseous lesions. ABC is most commonly associated with solitary or unicameral bone cyst, osteoclastoma, osteosarcoma, nonosteogenic fibroma, benign osteoblastoma, haemangioendothelioma and haemangioma of bone.
- Struthers and Shear (1984)hypothesized that ABC forms as a secondary phenomenon, which may develop by breakdown of a pre-existing lesion in bone. The initiating change in primary lesion appears to be the microcyst formation.
- Four phases of pathogenesis are recognized, which are as follows:
 1. Osteolytic initial phase.
 2. *Active growth phase* includes rapid destruction of bone and subperiosteal blow-out pattern.
 3. Mature stage: It is also known as 'stage of stabilization', which is

manifested by the formation of distinct peripheral bony shell and internal bony septa that produce the classic soap-bubble appearance.

4. *Healing phase* shows progressive calcification and ossification of the cyst.

Clinical features

- It occurs in two forms:
 1. Primary ABC: No pre-existing bone lesion is seen.
 2. Secondary ABC: Well-recognized pre-existing bone lesion is present.
- **Age.** <20 years.
- **Gender.** Female predilection.
- **Location.** Mandible, long bones.
- **Signs and symptoms**
 - The lesions are usually tender, particularly upon motion and this soreness may limit movement of the affected bone.
 - Swelling over the area of bone involvement is common.
 - Paraesthesia, compressibility, crepitus, malocclusion, mobility and resorption of involved teeth are common.
 - Upon surgical exposure of the lesion, excessive bleeding is encountered and appears as a *blood welling up* from the tissue. Tissue resembles as a blood-soaked sponge with large pores.

Radiographic features

Lesion may appear as a unilocular, honeycomb or soap-bubble radiolucent areas that cause expansion, perforation or even destruction of bone.

Histopathology

- It consists of a fibrous connective tissue stroma containing many cavernous or sinusoidal blood-filled spaces. Usually, these blood-filled spaces are not lined by endothelium.
- Numerous young fibroblasts and patchy distribution of multinucleated giant cells are seen in the connective tissue stroma.
- Commonly, varying amount of haemosiderin pigments and osteoid formation are seen.

Differential diagnosis

- Fibrous dysplasia
- Interosseous haemangioma
- Traumatic bone cyst

Prognosis and predictive factors

- Surgical curettage or excision is the treatment of choice.
- Recurrence is rare.

Cysts associated with the maxillary antrum

Cysts associated with the maxillary antrum are given in Table 5.1.

Table 5.1

Cysts associated with the maxillary antrum

Mucocele	It occupies the entire sinus. Cystic structure filled with mucus and lined by antral epithelium. It is associated with blockage of the ostium and may be secondary to chronic sinusitis. It may destroy and perforate adjacent bone.
Retention cyst	Epithelial lined cyst caused by mucus retention as a result of blockage of a duct. Often, small and clinically silent and found associated with thickened mucosa in sinusitis or in polyps. Dome-shaped radiopacity on the antral wall may be indistinguishable from a pseudocyst or polyp.
Pseudocyst	Inflammatory in origin, usually caused by accumulation of exudates that raise the mucosa from the bone of the antral floor. Most often, secondary to odontogenic infection. Dome-shaped radiopacity may be seen on the sinus floor.
Postoperative maxillary cyst	Secondary to an operative procedure. Most often due to Caldwell–Luc incision into the antrum or osteotomy. Probably arises from entrapped antral lining. True cyst filled with mucus and lined by antral epithelium

Mucocele

Definition

Cystic lesions developing from the salivary glands are commonly known as *mucocele*. These cysts will commonly develop in relation to the minor salivary glands. Mucocele includes both *mucous extravasation cysts* and *mucous retention cysts.*

- *Mucous extravasation cysts:* Lesions in which mucin is extravasated into the connective tissue and is devoid of epithelial lining (pseudocyst).
- Mucous retention cysts: Lesions in which mucin is retained in the dilated salivary excretory duct and is lined by epithelium (true cyst).

Pathogenesis

Pathogenesis of mucocele is illustrated in Figure 5.10.

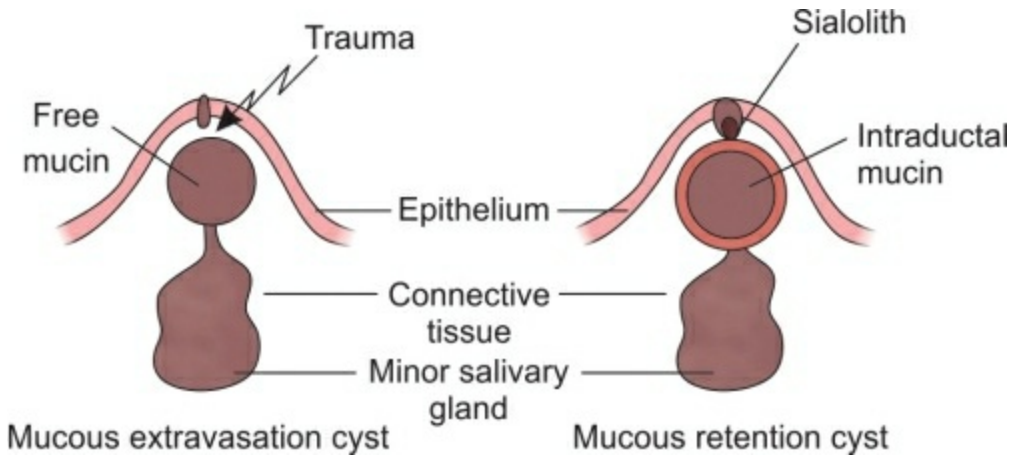


FIG. 5.10 Pathogenesis of mucocele: Mucous extravasation cyst (left) showing free mucin in the connective tissue because of ductal damage by a trauma and mucous retention cyst (right) showing mucin retained in the salivary excretory duct because of blockage by a sialolith.

Clinical features

- **Age.** 10–60 years.
- **Gender.** No gender predilection.
- **Location.** Lower lip.
- **Signs and symptoms**
 - Usually, painless, round or oval-shaped, recurrent swelling occurs on lower lip.
 - The swelling may develop suddenly at mealtimes and many drain spontaneously at intervals.
 - Some patients are able to relate the development of cyst due to trauma.
 - Usually, mucocele is 1–2 mm in diameter but sometimes it may reach up to 10 mm in diameter.
 - The superficial lesions are blue and fluctuant while the deeper lesions have the colour of normal mucosa.

Histopathology

- Microscopically, three distinct morphological patterns are seen. The first two patterns represent *mucous retention cysts* and the third pattern represents *mucous extravasation cyst*.
- **Mucous retention cysts** (well-defined cysts) comprise of two groups:
 1. The periphery of the lesion consists of granulation tissue or condensed fibrous tissue or both and is infiltrated by vacuolated macrophages, lymphocytes and polymorphonuclear leukocytes. One

or more dilated ducts may be present and sometimes a breach may be seen in a duct.

2. The cysts may be partially or completely lined by epithelium. It may consist of one or two layers of flattened cells, cuboidal cells, stratified squamous epithelium or pseudostratified columnar epithelium.

- **Mucous extravasation cysts** (poorly defined cysts) (Fig. 5.11) consist of poorly defined pools containing eosinophilic mucinous material with numerous vacuolated macrophages—*mucinophages*. Usually, these cysts will be small in size but some lesions may extend widely in the connective tissue.

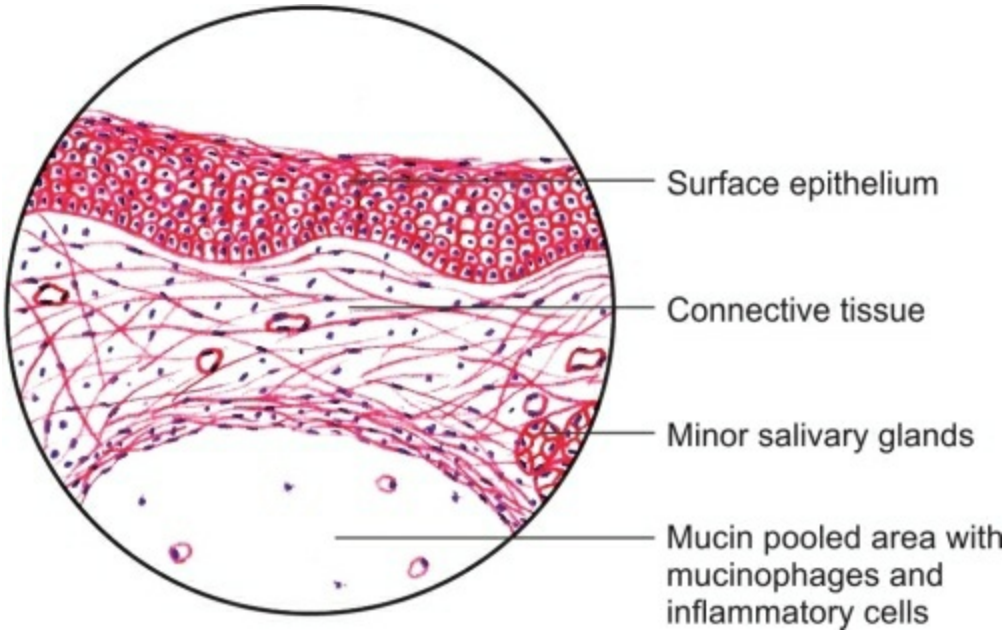


FIG. 5.11 Mucous extravasation cyst.

Differential diagnosis

- Salivary gland tumours, e.g. adenoid cystic carcinoma
- Lipoma
- Fibroma

Prognosis and predictive factors

- Most of the lesions are chronic in nature and local surgical excision will be necessary.

- Few mucoceles are short-lived lesions that rupture and heal by themselves.
- To minimize the risk of recurrence, the surgeon should remove adjacent minor salivary glands also.

Ranula

Definition

The ranula is a form of mucocele but larger in size, which specifically occurs in the floor of the mouth in association with the ducts of the submaxillary or sublingual gland. *Ranula* means *frog's belly.*

Pathogenesis

- Sialolith formation.
- Duct compression due to trauma or from a growing tumour in the vicinity.
- Atresia (absence of the duct).
- Scar or stricture formation to the duct (postsurgical complication).

Clinical features

- **Age.** 20–40 years.
- **Gender.** No gender predilection.
- **Location.** Floor of the mouth.
- **Signs and symptoms**
 - It usually appears as a dome-shaped, soft, fluctuant, unilateral swelling in the floor of the mouth.
 - The lesion is generally larger in size, which fills floor of the mouth and deviates the tongue.
 - Usually, ranula appears bluish translucent but deeper lesions may be normal in colour.
 - *Plunging or* cervical ranula: An unusual variant occurs when the spilled mucin dissects through the mylohyoid muscle and produces swelling within the neck.
 - Someranulas rupture spontaneously and release mucin content into the mouth.

Radiographic features

- Not significant.
- Sialolith can be elicited in occlusal radiograph.

Histopathology

- It appears similar to the smaller mucous retention cyst, which is surrounded by a fibrous connective tissue wall or granulation tissue.
- Multiple foamy histiocytes are often seen in the granulation tissue capsule.

Differential diagnosis

- Dermoid cyst
- Benign lymphoepithelial cyst

Prognosis and predictive factors

The aetiological factor has to be removed to eliminate the possibility of further recurrence. In case of repeated recurrences, the involved gland has to be excised.

Developmental cysts of the head and neck

Developmental cysts of the head and neck comprise of *thyroglossal duct cysts*, *dermoid and epidermoid cysts*, *branchial cleft cysts* and *intraoral lymphoepithelial cysts.*

Thyroglossal duct cyst

- Thyroglossal cyst develops from remnants of thyroglossal duct.
- The exact aetiology for stimulation of remnants to form cyst is unknown. The inflammatory conditions which form reactive hyperplasia of the lymphoid tissue adjacent to the remnants of thyroglossal duct may stimulate the epithelial remnants.

Clinical features

- **Age.** <10 years.
- **Gender.** No gender predilection.
- **Location**
 - *Extraoral lesions:* Midline of the neck in the area of the hyoid bone.
 - *Intraoral lesions:* Floor of the mouth.
- **Signs and symptoms**
 - The cyst presents as a soft, painless, fluctuant, movable swelling, unless it is complicated by secondary infection.

- If the cyst maintains an attachment to the hyoid bone or tongue, it will move vertically during swallowing or protrusion of the tongue.
- If the cysts are located high in the tract, they may cause dysphonia or dyspnoea.

Histopathology

- The cysts are lined by ciliated pseudostratified columnar epithelium or stratified squamous epithelium.
- Frequently, thyroid tissue is seen in the fibrous capsule.
- The cysts located in the lingual area show mucous cells in the cyst lining and seromucous glands in the capsule.
- Sometimes, lymphoid tissue with prominent germinal centres is seen.

Prognosis and predictive factors

- Surgical excision of cyst with tract and its branches is recommended.
- Recurrence is rare.

Dermoid and epidermoid cysts

- **Dermoid cysts** are developmental cysts arising from entrapped ectodermal tissue which is lined by epidermis with skin appendages in the fibrous capsule. It is generally classified as a benign cystic form of teratoma.
- **Epidermoid cysts** are similar cysts lined by epidermis, but without appendages in the fibrous capsule.

Pathogenesis

- *Dermoid cyst*
 - Unknown.
 - Intermingling of stomatodeal ectoderm and endoderm at the 32nd day of IU life.
 - The sequestration of skin and subsequent implantation of it along the lines of embryonic closure.
- *Epidermoid cyst*
 - Sequestration and implantation of epidermal rests during embryonal period.
 - Occlusion in pilosebaceous unit or in eccrine ducts.
 - Iatrogenic or surgical implantation of epithelium into the jaw.

- Syndromes: Gardner syndrome, basal cell naevus syndrome and pachyonychia congenita.

Clinical features

- **Age.** 15–35 years.
- **Gender.** Male predilection.
- **Location.** The floor of the mouth.
- **Signs and symptoms**
 - The intraoral swelling lifts the tongue and may lead to difficulty in speaking, eating, breathing or closing the mouth.
 - Deeper lesions between the geniohyoid and mylohyoid muscles produce a submental swelling in the neck giving the patient a *double-chin appearance*.
 - The swelling may feel doughy or fluctuant.

Histopathology

- Usually, both dermoid and epidermoid cysts are lined by orthokeratinized stratified squamous epithelium resembling epidermis.
- The dermoid cyst capsule is characterized by the presence of one or more dermal appendages such as hair follicles, sweat glands or sebaceous glands. Hair is very rarely found. The lumen is usually filled with keratin.
- Epidermoid cysts contain abundant keratin in the lumen with no dermal appendages in the capsule.

- *Teratoid cyst:* A cystic form of teratoma that contains a variety of germ layer derivatives:
 - Skin appendages include hair follicles, sebaceous glands and sweat glands.
 - Connective tissue elements, e.g. muscle, blood vessels and bone.
 - Endodermal structures, e.g. gastrointestinal lining.

Note: Intraoral epidermoid cysts should not be confused with the more common epidermoid cyst of the skin, which is a nonteratomatous lesion

that arises from the hair follicle.

Prognosis and predictive factors

- Surgical excision is the mainstay in the management protocol and recurrence is seldom noticed.

Key points

- *Cyst* is a pathological cavity having fluid, semifluid or gaseous contents and it is not created by the accumulation of pus. It is frequently, but not always, lined by epithelium.
- *Keratocystic odontogenic tumour* is a benign intraosseous tumour of odontogenic origin, characterized by parakeratinized stratified squamous epithelial lining and potential aggressive, infiltrative behaviour.
- *Naevoid basal cell carcinoma syndrome* includes multiple naevoid basal cell carcinomas and OKCs, bifid ribs, ectopic calcifications, plantar and palmar pits, central nervous system and ocular lesions and other congenital skeletal defects.
- *Gingival cyst of infants* is small, superficial, keratin-filled cysts that are found on the alveolar mucosa of infants that resolve without treatment.
- *Bohn's nodules* are scattered over the hard palate, often near the soft palate junction.
- *Epstein's pearls* occur along the mid-palatine raphe of the hard palate.
- *Lateral periodontal cyst* is a slow-growing, nonexpansile developmental odontogenic cyst derived from one or more rests of the dental lamina, comprising of embryogenic lining of one to three cuboidal cells and distinctive focal thickenings (plaque).
- *Gingival cyst of adults* represents a small developmental odontogenic cyst of the gingival soft tissue derived from the rests of the dental lamina, containing a lining of embryonic epithelium of cuboidal cells and distinctive focal thickenings.
- *Ghost cells* may occur in calcifying odontogenic cyst, craniopharyngioma, calcifying epithelioma of Malherbe, dentinogenic ghost cell tumour and ghost cell odontogenic carcinoma.
- *Radicular cysts* are the most common inflammatory cysts and arise from the epithelial residues in the periodontal ligament as a result of periapical periodontitis following death and necrosis of the pulp (nonvital tooth).

- *Residual cyst* is a radicular cyst that is retained in the jaws after the removal of offending nonvital tooth.
- *Mucous extravasation cyst:* Mucin is extravasated into the connective tissue and it is devoid of epithelial lining (pseudocyst).
- *Mucous retention cyst:* Mucin is retained in the dilated salivary excretory duct and it is lined by epithelium (true cyst).

Frequently asked questions

1. Classify odontogenic cysts and discuss pathogenesis, clinical features, radiographic features and histopathology of odontogenic keratocyst.
2. Dentigerous cyst.
3. Bohn's nodules and Epstein's pearls.
4. Discuss pathogenesis, clinical features and histopathology of lateral periodontal cyst.
5. Glandular odontogenic cyst.
6. Calcifying odontogenic cyst.
7. Ghost cells.
8. Nasolabial cyst.
9. Discuss pathogenesis, clinical features, radiographic features and histopathology of radicular cyst.
10. Rushton bodies.
11. Cholesterol clefts.
12. Solitary bone cyst.
13. Aneurysmal bone cyst.
14. Mucocele/mucous extravasation cyst/mucous retention cyst.
15. Dermoid cyst and epidermoid cyst.

CHAPTER 6

Bacterial, viral and fungal infections of the oral cavity

Bacterial infections

Scarlet fever

Scarlet fever is a highly contagious systemic infection, caused by β-haemolytic streptococci, *Streptococcus pyogenes.*

Pathogenesis

- *S. pyogenes* produces an exotoxin or erythrogenic toxin which affects blood vessels.
- Skin rashes are produced by vasodilatation and consequent hyperaemia.
- The incubation period is 1–7 days.

Clinical features

- **Age.** 3–12 years.
- **Sex.** Female predilection.
- **Location.** Tonsils, pharynx, soft palate and tongue.
- **Signs and symptoms**
 - The patient exhibits severe pharyngitis, tonsillitis, headache, chill, fever, abdominal pain and vomiting.
 - Enlargement and tenderness of regional lymph nodes are seen.
 - *Skin*
 - After 2–3 days of disease, it produces bright scarlet skin rashes at the skin folds which is called *Pastia lines.*
 - The skin rashes vary in colour from scarlet to dusky red and the sandpaper-like texture on palpation. This classic feature of rashes is described as *sunburn with* goose pimples.
 - These rashes undergo desquamation after 1 week. The period of whole desquamation process takes 3–8 weeks.
 - *Oral manifestations (stomatitis scarlatina)*
 - Tonsils show erythematous and oedematous appearance, sometimes it may be covered with yellowish exudate.
 - Petechiae may be scattered on the soft palate, hard palate and uvula. These spots are called as *Forchheimer spots.*
 - During the 2nd day of disease course, white coat of tongue through which oedematous, hyperaemic fungiform papillae can be appreciated is called *white* strawberry tongue. By the 4th to 5th day,

the white coat disappears and becomes deep red, smooth and glistening tongue except papillae called *raspberry tongue* or *red strawberry tongue*.

- Sometimes, ulceration of the buccal mucosa and palate is present due to secondary infection.

Diagnosis

- Routine blood examination: Increased neutrophils, leucocytosis, increased erythrocyte sedimentation rate and C-reactive protein are seen.
- Microbial culture of throat or pharyngeal secretions.

Prognosis and predictive factors

- There is no method for prevention of disease but there is preventive method for the complication from the disease.
- Administration of antibiotics like penicillin, dicloxacillin, cephalexin with ameliorate, erythromycin, if the patient is allergic to penicillin.
- ***Complications***
 - Peritonsillar abscess
 - Mastoiditis
 - Meningitis
 - Pneumonia
 - Glomerulonephritis

Tuberculosis

Tuberculosis (TB) is a chronic infection, primarily affecting the lungs, caused by the bacterium called *Mycobacterium tuberculosis.*

Microorganisms

- *M. tuberculosis* is a rod-shaped, aerobic, non-motile, nonspore-forming and slow-growing bacterium.
- *M. tuberculosis* is called acid-fast bacilli due to the fact that once stained it cannot be decolourized by acid alcohol. This acid fastness is due to high content of *mycolic acids*, a long-chain cross-linked fatty acid and other cell wall lipids.
- *Atypical tuberculosis* is caused by *M. bovis.*
- In patients with AIDS, *M. avium intracellulare* is a common cause for

opportunistic infection.

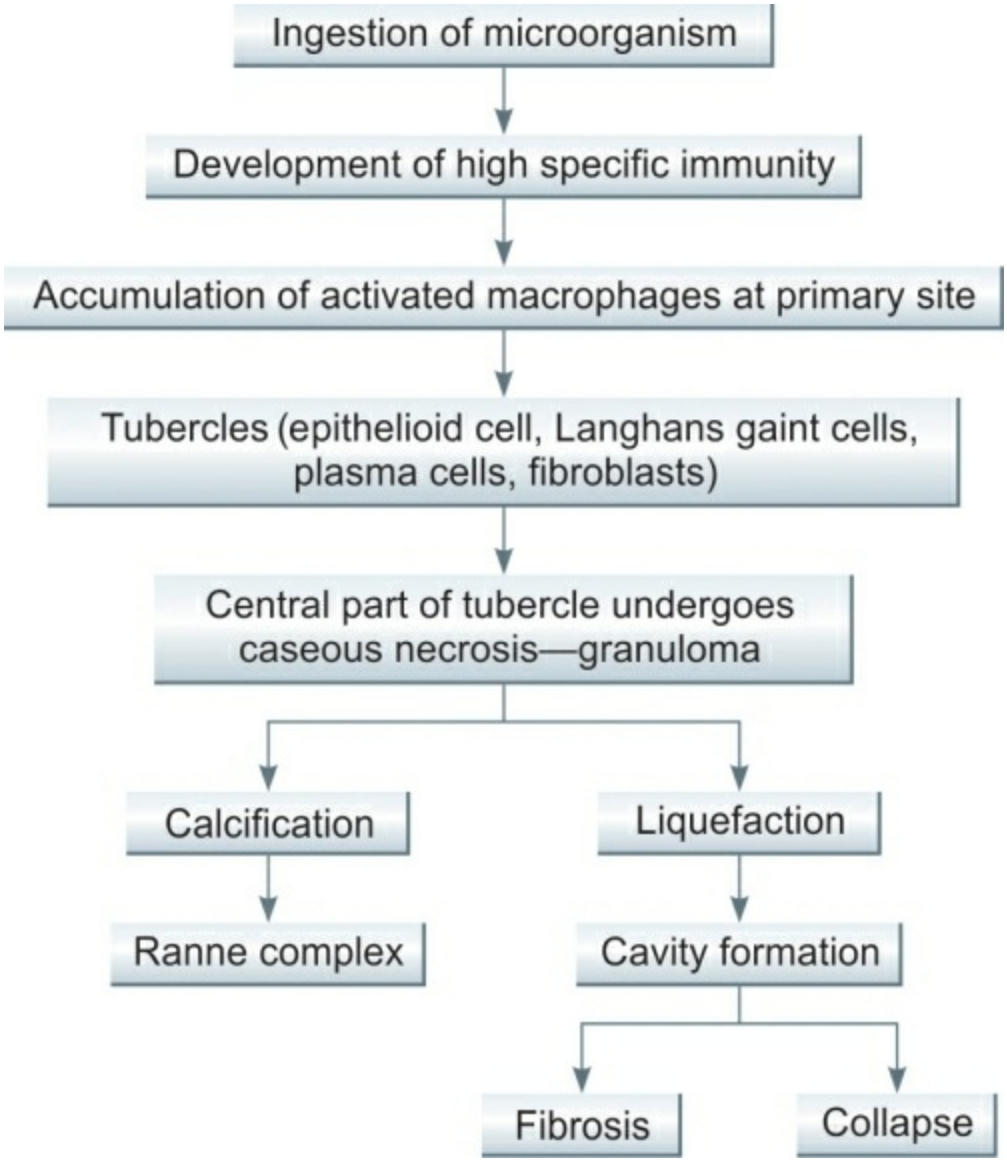
Mode of transmission

- Tuberculosis is spread usually from person to person through air-borne droplets or oral mucosa.
- Atypical tuberculosis is transmitted by drinking unpasteurized milk.

Pathogenesis

- The pathogenesis of tuberculosis is illustrated in Flowchart 6.1.
- Microorganism of tuberculosis is transmitted from person to person via air-borne infectious droplets, i.e. when a person with tuberculosis infection coughs, sneezes or talks, tiny droplets of saliva or mucus are expelled into the air, which can be inhaled by another healthy person. Less frequently, the disease can be caused by ingesting unpasteurized cow milk infected with *M. bovis* or other atypical mycobacteria.
- Once infectious particles reach the alveoli, macrophages engulf the TB bacteria. The bacteria get multiplied and grow within themselves resulting in change in shape and size of the cell which appears as a epithelial like cell or *epithelioid cells.*
- The epithelioid cells fuse together and form *Langhans type of giant cells* with horseshoe pattern of arrangement of nuclei.
- Epithelioid cells, Langerhans cells, lymphocytes and fibroblasts together form *tubercles.* As the disease progress, the central part of the tubercles undergoes necrosis.
- Lymphocyte and fibroblast accumulate around the caseous necrosis which result in a localized, fibrocalcified nodule at the initial site of involvement and termed as *granuloma.*
- *Primary tuberculosis:* Tuberculosis occurs in unexposed people and always involves the lung and spreads through air-borne droplet from the patient. Microorganism may be viable and remains dormant for years to life.
- *Secondary tuberculosis:* Reactivation of organisms occurs in previously exposed people and always involves the lung. It is always associated with compromised host defence. Oral tuberculosis usually results from secondary inoculation of oral mucosa breached by any type of ulceration or by minor masticatory trauma by infected sputum or by haematogenous dissemination from other infected sites.
- Diffuse dissemination of infection through the vascular system may occur and often produces multiple small foci of infection in various organs,

which is known as *miliary tuberculosis.*



FLOWCHART 6.1 Pathogenesis of tuberculosis

Clinical features

- **Primary tuberculosis:** Asymptomatic, but few may present febrile illness, cough, which may be dry or productive.
- **Secondary tuberculosis**
 - Low-grade fever, malaise, anorexia, weight loss, night sweats, productive cough with haemoptysis and chest pain.
 - Progressive TB may lead to wasting syndrome—*consumption,* because it

appeared that the patient's body is being consumed or destroyed.
 - It is often associated with immunosuppressive medications, diabetes, old age, poverty and crowed living conditions.
- **Miliary tuberculosis**
 - Common in children: Acute febrile illness.
 - Adults: More insidious with gradual development of ill health, anorexia, loss of weight and fever.
 - Bilateral crackles on auscultation, hepatosplenomegaly and lymphadenopathy.
 - Choroid tubercles are seen in children but rare in adults.
- **Extrapulmonary tuberculosis**
 - Site: Lymphatic system, skin, skeletal system, CNS, kidney and GIT.
 - More than 50% of AIDS patients are affected.
 - Involvement of skin: *Lupus vulgaris frequently* appears as papular nodules which ulcerates.
- **Oral manifestations**
 - It is unclear whether lesions develop from haematogenous spread or from exposure to infected sputum.
 - Primary oral tuberculosis: Gingiva, mucobuccal fold and areas of inflammation adjacent to teeth or in extraction site.
 - Secondary oral tuberculosis: Tongue, palate and lip.
 - *Tuberculosis gingivitis:* Diffuse, hyperaemic, nodular or papillary proliferation of gingival tissue.
 - Oral TB ulcers are usually painless, single rather than multiple, indurate, irregular, undermined margin and a necrotic base. These ulcers may be covered by pseudomembrane.
 - Enlargement of salivary glands is common.
- **TB of maxilla or mandible:** Common entry of microorganisms is into an area of periapical inflammation by way of bloodstream—*anachoretic effect*. Moreover, direct immigration through pulp chamber and root canal of a tooth with an open cavity and also from tooth extraction socket.
- **TB periapical granuloma or tuberculoma:** These lesions are painful and involve considerable amount of bone by rapid extension.
- **TB osteomyelitis of the jaws:** It results in sinus or fistula formation, trismus and paraesthesia.
- **Scrofula:** It is characterized by enlargement of lymphoid tissue due to tuberculosis infection caused by drinking contaminated milk.
- Enlargement of regional lymph nodes and becomes matted in appearance

and rubbery in consistency. Later, it may lead to abscess and sinus formation.
- Later, calcification occurs in the infected nodes.
- Rarely, TB tonsillitis occurs.

Histopathology (fig. 6.1)

- Granuloma or tubercle shows collection of epitheloid histiocytes, lymphocytes, Langhans multinucleated giant cells with central caseous necrosis and peripheral fibrous tissue.
- Sometimes, there may be areas of dystrophic calcification.
- Special stain such as Ziehl–Neelsen or acid-fast stain should be used to demonstrate the mycobacteria.

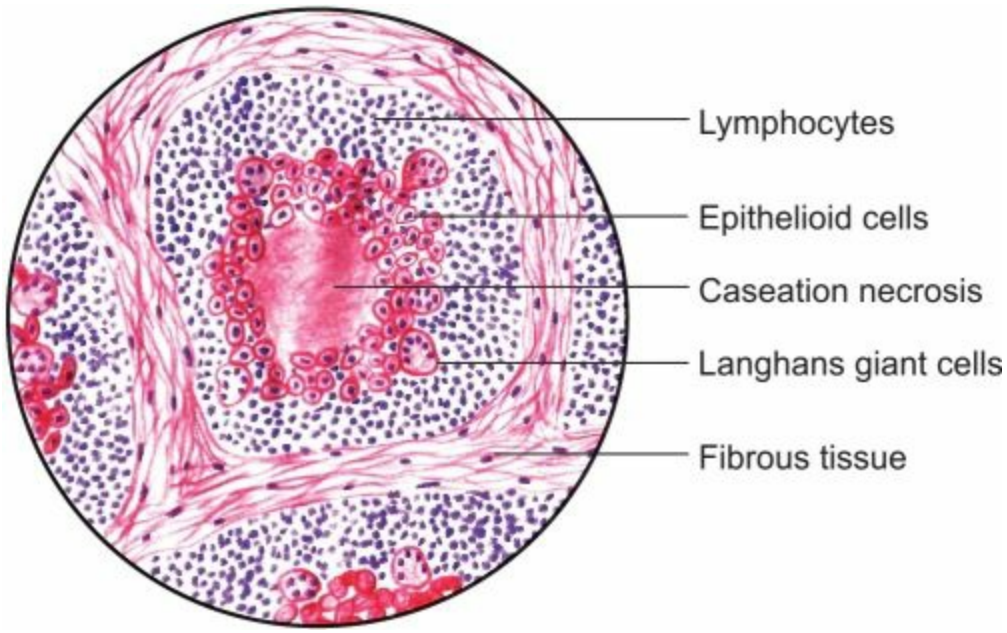


FIG. 6.1 Tubercle in tuberculosis.

Diagnosis

Imaging techniques

- Radiographs of chest.
- CT scan: Mediastinal or hilar lymphadenopathy, cavities and intralesional calcification.
- MRI scan: Extrapulmonary TB.

Histopathological smear

- Presence of acid-fast bacilli (AFB) in sputum smear is the standard for diagnosis of TB.
- Respiratory specimen: Sputum samples are collected early morning. Laryngeal swab, transtracheal aspirations, bronchoalveolar lavage and gastric contents aspiration by nasogastric tube in children.
- WHO defines any patient whose sputum smear is positive for acid-fast bacilli as case of pulmonary TB.
- AFB is stained by the following methods:
 - Ziehl–Neelsen (Z–N) staining
 - Kinyoun's cold staining methods
 - Rhodamine staining for fluorescent staining

A minimum of five AFB on fluorescent microscopy and three on Z–N staining is reported as positive.

Culture

- Commonly used media are:
 - Lowenstein–Jensen medium
 - Agar-based media like middle brook medium

It takes 4–6 weeks for the growth of *M. tuberculosis.*

- Other faster methods are:
 - *Rapid slide culture technique:* Growing *mycobacterium* on slides and examining microculture under microscope.
 - *Radiometric culture method:* Based on utilization of radioisotope of carbon by *mycobacterium*.

Tuberculin test (Mantoux test)

- It is used to determine if someone has developed, an immune response to the *M. tuberculosis* bacterium. This response can occur if someone currently has TB, if they were exposed to it in the past or if they received the Bacillus Calmette–Guerin (BCG) vaccine against TB.
- The tuberculin skin test which is based on *M. tuberculosis* bacterium produces a delayed-type hypersensitivity skin reaction.
- Subcutaneous injection of 0.1 ml of five tuberculin units of purified protein derivative (PPD) of Seibert stabilized with Tween 80 or one tuberculin unit of PPDRT 23 into forearm is done.
- The reaction in the skin to tuberculin PPD begins as the immune system releases chemical messengers called *lymphokines.*
- These lymphokines induce induration (a hard, raised area with clearly defined margins at and around the injection site) through local vasodilatation (expansion of the diameter of blood vessels) leading to

fluid deposition known as oedema, fibrin deposition, and recruitment of other types of inflammatory cells to the area.
- It is positive, if induration is seen after 48–72 hours.
- Maximum diameter of induration is measured by palpation, but not redness.
- Interpretation:
 - >15 mm or ulceration: Strongly positive
 - >10 mm: Positive
 - 5–9 mm: Indeterminate
 - <5 mm: Negative
- Tuberculin skin test is a screening test, not a diagnostic test.
- False negativity is seen in tuberculosis pleurisy, military TB, immunosuppressed conditions and viral herpes.

Recent advances
- Radioimmunoassay (RIA)
- Soluble antigen fluorescent antibody (SAFA) test
- Enzyme-linked immunosorbent assay (ELISA)
- Antibody assay to detect the release of interferon gamma

Prognosis and predictive factors
- Inactive tuberculosis may be treated with antibiotics, isoniazid (INH), to prevent the TB infection from becoming active.
- Active TB is treated by INH, rifampin and pyrazinamide for 8 weeks or INH and rifampin for 16 weeks.
- Extensively drug resistant TB (XDR TB) can be treated using ethambutol and streptomycin as first-line medication.
- XDR TB is resistant to most of the antituberculous drugs. The treatment outcome is usually worse, particularly in patients with impaired immune system such as in HIV infection.
- *BCG vaccine* for TB is available.

Leprosy

(Synonym: Hansen's disease)
- Leprosy is an infectious disease; the term is derived from the French word *leper* and Greek word *lepros* which means *scaly* or *scales.*
- Leprosy is a chronic granulomatous disease caused by the bacteria *Mycobacterium leprae*, which causes damage to the skin and the peripheral

nervous system.

Microorganisms

- *Mycobacterium leprae* is a rod-shaped bacillus, which is an obligate intracellular (only grows in certain human and animal cells) bacterium.
- It is an *acid-fast* bacterium because of its chemical characteristics. When special stain like Ziehl–Neelsen stain is used, it stains red on a blue background due to mycolic acid content in its cell walls.
- The bacteria grow best at 80.9–86°F, so cooler areas of the body tend to develop the infection.

Pathogenesis

- Human-to-human transmission by respiratory droplets at nasal or oropharyngeal mucosa is the primary source of infection.
- Both cell-mediated and humoral responses are elicited by bacterial antigen DNA glycolipids.
- *Lipoarabinomannan,* a component of cell membrane, induces immune suppression by inhibiting the interferon gamma-mediated activation of macrophages.
- The bacteria grow very well in the body's macrophages and Schwann cells, which results in inflammatory response.

Classification

- Leprosy manifests in three forms:
 1. Tuberculoid leprosy
 2. Borderline leprosy
 3. Lepromatous leprosy
- *Ridley–Jopling system* consists of six forms:
 1. Indeterminate leprosy
 2. Tuberculoid leprosy
 3. Borderline tuberculoid leprosy
 4. Mid-borderline leprosy
 5. Borderline lepromatous leprosy
 6. Lepromatous leprosy
- *WHO (2009)* classification is based on the number of skin lesions:
 1. *Paucibacillary leprosy (tuberculoid leprosy):* Skin lesions with no bacilli (*M. leprae*) are seen in skin smear.

2. *Multibacillary leprosy (lepromatous leprosy):* Skin lesions with bacilli (*M. leprae*) are seen in skin smear.

Clinical features

- **Age.** Children.
- **Sex.** Male predilection.
- **Location.** It affects the peripheral nerves, upper respiratory tract, eyes, testis, muscle, bone, joints, mucous membranes and skin, especially the cool places on the body (e.g. eyes, nose, earlobes, hands, feet and testicles).
- **Signs and symptoms**
 - *Tuberculoid leprosy*
 - It corresponds to *paucibacillary type of leprosy.*
 - It is the mild form of leprosy.
 - Organism not found in the skin lesions.
 - Localized form.
 - Lepromin test is positive.
 - Incubation period is 2–5 years.
 - One or more light or slightly red patches of skin that appear on the trunk or extremities.
 - Severe pain.
 - Muscle weakness, especially in the hands and feet.
 - Skin stiffness and dryness.
 - Loss of sweating.
 - Loss of fingers and toes.
 - Blindness.
 - Enlarged nerves, especially those around the elbow (ulnar nerve) and knee (peroneal nerve).
 - *Borderline leprosy:* Features of both tuberculoid and lepromatous leprosies are present.
 - *Lepromatous leprosy*
 - It corresponds to *multibacillary type of leprosy*.
 - It is the severe form of the disease.
 - Many organisms found in the skin lesions.
 - Diffuse and generalized form.
 - Lepromin test is positive.
 - Incubation period is 8–12 years.
 - Numerous, symmetrical with ill-defined, varying in size,

hypopigmented macules or papule found on the face, ears, wrists, elbows, knees and buttocks.
 - Thinning of eyebrows and eyelashes.
 - Thickened skin on the face can lead to a distorted facial appearance (leonine facies).
 - Nasal stuffiness, nasal bleeding, loss of smell sensation.
 - Collapsing of the nasal bridge.
 - Loss of sweat.
 - Laryngitis.
 - Facial paralysis.
 - Swelling of the lymph nodes in the groin and armpits.
 - Scarring of the testes leads to infertility.
- **Oral manifestations**
 - Site: Hard palate, soft palate, facial gingiva, tongue, lips, and buccal mucosa.
 - Yellowish to red, sessile, firm, enlarging papule that develops ulceration and necrosis.
 - Underlying bone erosion is seen.
 - Complete loss of uvula and fixation of soft palate.
 - *Facies leprosa*
 - Atrophy of the anterior nasal spine
 - Atrophy of the anterior maxillary alveolar ridge
 - Endonasal inflammatory changes
 - *Teeth:* Loss of teeth, hypoplasia of teeth, short tapering root and discoloured tooth.
 - Perforation of the palate.
 - Unilateral or bilateral facial paralysis.

Histopathology

- **Tuberculoid leprosy:** Well-formed granulomatous inflammation with clusters of epithelioid histiocytes, lymphocytes and multinucleated giant cells are seen.
- **Lepromatous leprosy:** There are no well-defined granulomas but it contains sheets of lymphocytes intermixed with vacuolated histiocytes known as *lepra cells.*

Diagnosis

- Skin smears or biopsy material that show acid-fast bacilli with the Ziehl–

Neelsen stain or the Fite stain (biopsy)
- Lepromin test
- Foot culture histamine test
- ELISA
- Molecular biological technique like PCR

Prognosis and predictive factors

- **Chemotherapy**
 - Tuberculoid leprosy: 6 months regimen of dapsone and rifampicin.
 - Lepromatous leprosy: 24 months regimen of dapsone, rifampicin and clofazimine.
 - Patients allergic to rifampicin are treated with 24 months course of clofazimine, ofloxacin and minocycline.
 - Surgery and physiotherapy can be advised.
- ***Complications***
 - Cosmetic disfigurement
 - Muscle weakness
 - Loss of fingers or toes
 - Blindness
 - Arthritis
 - Amyloidosis

Actinomycosis

Actinomycosis is a chronic bacterial infection caused by *Actinomyces* species. Most of the lesions are caused by *A. israelii, A. viscosus* and the remaining like *A. naeslundii, A. odontolyticus, A. meyeri, A. gerencseriae* and A. propionibacterium propionicum cause the infection less frequently.

It is characterized by chronic suppurative and granulomatous inflammation, and formation of multiple abscesses and sinus tracts that may discharge sulphur-like granules.

The most common clinical forms of actinomycosis are cervicofacial (i.e. lumpy jaw), thoracic and abdominal.

Microorganisms

Filamentous, gram-positive, non-acid-fast, anaerobic-to-microaerophilic bacteria.

Pathogenesis

- Actinomycetes enter the facial tissues after trauma, surgery or infection, i.e. they enter through the break in the integrity of the mucous membranes, periodontal pocket and extracted socket.
- The common triggering causes are dental abscess, oral surgery or intrauterine devices.
- The bacteria produce the infection by elaborating a toxin or enzyme or by inhibiting host defences.
- Once the infection is established, there is intense inflammatory response (i.e. suppurative, granulomatous) and fibrosis; later it invades the surrounding tissues or organs and produces draining sinus tracts.
- The infection does not spread through heamatogenous or lymphatic dissemination, but it occurs by direct soft tissue extension.

Clinical features

- **Age.** 20–50 years.
- **Sex.** Male predilection.

It may be acute lesions, rapidly progressive infection or chronic lesions, slowly progressive infection that is associated with fibrosis.

Cervicofacial actinomycosis

- Cervicofacial actinomycosis is the most common type of the infection, comprising 50–70% of reported cases.
- It occurs in the mouth, salivary gland, skin of the face and neck.
- The bacterium enters through the periodontium (the tissues surrounding and supporting the teeth), soft tissue wounds and salivary gland ducts.
- It is believed that infection may arise after a tooth extraction, from tooth decay or abscess, as a part of periodontal disease, from a non-penetrating jaw trauma, poor dental hygiene and mucosal injuries.
- Fever, weight loss, malaise and cough are seen.
- It is characterized by soft tissue swelling and induration of the tissue, i.e. it forms an abscess, red to reddish-purple in colour, and gives hard to fluctuant (wood-like) in consistency with minimal or no pain.
- The abscess breaks through the skin surface to produce a draining sinus tract.
- Development of fistulas (sinus tracts) that discharge purulent material containing granules with a yellow sulphur-like appearance (termed *sulphur granules*).

Note: Another infection producing sulphur-like granules is *botryomycosis.*

- Sinus through which abscess has drained to heal but because of chronicity of disease a new abscess develops and perforates. Thus, patient shows scaring and disfigurement of skin.
- Infection does not spread along facial plans, lymphatics and vascular routes.
- Localized abscess without fibrosis is seen in tongue.
- Soft tissue infection may extend to mandible or maxilla resulting in actinomycotic osteomyelitis. Radiographically, it shows ill-defined area of radiolucency with radiopaque border. Later, it may invade into the cranium, spine and thorax.

Thoracic actinomycosis

- Thoracic actinomycosis accounts for 15–25% of cases.
- It involves the lungs and mediastinum (region between the two lungs).
- Fever, cough, sputum production, loss of weight, night sweats and shortness of breath are seen.
- It represents as mass, which spreads to involve the pleura, pericardium and chest wall leading to the formation of sinuses that discharge sulphur granules.

Abdominal actinomycosis

- Actinomycosis of the abdomen and pelvis accounts for 10–20% of reported cases.
- Infection usually begins in the gastrointestinal tract and spreads to the liver and spleen.
- Fever, chills, intestinal colic, vomiting and weight loss are seen.
- A palpable mass and an external sinus are evident.

Histopathology (fig. 6.2)

- It shows granulomatous reaction with central abscess formation and characteristic colonies of microorganisms in it.
- These colonies appear to be floating in a sea of polymorphonuclear leukocytes, often associated with multinucleated giant cells and

macrophages particularly around the periphery of the lesion.

- The individual colony appears round or lobulated shape. It is made up of meshwork of haematoxyphilic filaments, but these filaments shows peripheral eosinophilic club-shaped ends. This peculiar appearance of the colonies with the peripheral radiating filaments insists to use the term *ray fungus*.
- The tissue surrounding the lesion exhibit fibrosis.

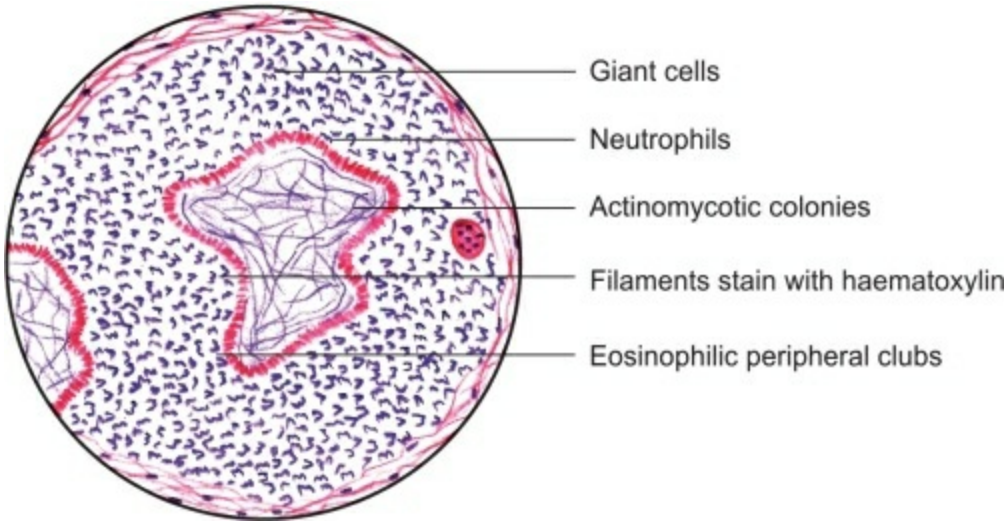


FIG. 6.2 Actinomycosis.

Diagnosis

- Culture of the tissue or fluid.
- Examination of drained fluid under a microscope shows sulphur granules and the *Actinomyces* species of bacteria.

Prognosis and predictive factors

- Surgical drainage or removal of the lesion.
- Antibiotics like penicillin, for several months to a year.
- If the condition is related to an IUD, the device must be removed.
- ***Complications:*** Meningitis.

Botryomycosis

(Synonyms: Actinobacillosis; bacterial pseudomycosis)

It is a rare chronic granulomatous bacterial infection that affects the skin, mucosa and sometimes the viscera. The name refers to its *grape-like granules* (*botryo*—grapes and *mykes*—fungus).

Pathogenesis

- The anatomic structure and sulphur granules of its lesion are similar to that of actinomycosis, so it was believed that *actinomycetes* are the causative organism.
- Later, in 1919, the bacterial origin of the infection was discovered. *Staphylococcus, Streptococcus, Escherichia, Pseudomonas, etc.* are the organisms that cause the infection.
- Its pathogenesis is not completely understood. However, it is usually described in individuals with impaired immunity or with an underlying disease such as diabetes mellitus, cystic fibrosis or HIV infection.

Clinical features

- It is usually a localized granulomatous infection of the skin or mucosa.
- The localized infection may closely mimic actinomycosis by producing a chronic granulomatous mass with multiple ulcers and sinuses.
- It may disseminate to involve liver, lungs or kidneys, in which case the disease is usually fatal.
- Intraorally, it usually involves tongue and presented clinically as a firm, nodular lesion. However, there were no sinuses present.

Histopathology

Chronic granulomatous nodules is characterized by the presence of suppurative foci which contain granules that resemble actinomycosis granules. However, eosinophilic, peripheral club formation is not seen.

Prognosis and predictive factors

- It is nonspecific due to variety of different microbes.
- Surgical intervention aid in cure.

Tetanus

(Synonym: Lock jaw)

Tetanus is an acute infectious disease of the nervous system characterized by

intense activity of motor neurons and resulting in severe muscle spasms. It is caused by the causative bacterium *Clostridium tetani.*

Microorganisms

- It is an anaerobic, gram-positive bacillus.
- The bacteria are found in two forms: As *a spore* (dormant) or as *a vegetative* cell (active) that can multiply.
- The spores are present in soil, dust and animal waste, and can survive for many years.
- The active bacterial cells release two exotoxins such as *tetanolysin* and *tetanospasmin.* The function of tetanolysin is unclear, but tetanospasmin is responsible for the disease.

Pathogenesis

- *Predisposing factors*
 - Frostbite, surgery, crush wound, acute injury
 - Abscesses, ulcers, gangrene
 - Abortion, during childbirth and IV drug users (site of needle injection)
- Tetanus occurs when a wound becomes contaminated with bacterial spores.
- Infection follows when spores become activated and develop into gram-positive bacteria that multiply and produce toxin (tetanospasmin).
- Tetanospasmin binds to motor nerves that control muscles, enters the axon and travels in it and reaches the body of the motor nerve in the spinal cord or brainstem.
- Then the toxin migrates into the synapse where it binds to presynaptic nerve terminals and inhibits or stops the release of certain inhibitory neurotransmitters (glycine and γ-aminobutyric acid).
- If tetanospasmin reaches the bloodstream or lymphatic vessels from the wound site, it can be deposited in many different presynaptic terminals resulting in the same effect on other muscles.

Clinical features

- **Age.** Any age.
- **Sex.** Male predilection.
- **Location.** Muscles of jaws, shoulder, back and larynx.
- **Signs and symptoms**

- It is common in warm climate, i.e. during summer and rural areas.
- Incubation period ranges from 3 days to 4 weeks.
- Severe, uncontrollable muscle spasms.
- Irritability and pain in the neck and shoulder muscles.
- Difficulty in swallowing.
- Lockjaw or trismus results from spasms of the jaw muscles.
- *Risus sardonicus:* It is a characteristic feature that results from facial muscle spasms.
- Arching of the back due to muscle spasms is known as *opisthotonus.*
- Spasms of the laryngeal muscles.

Prognosis and predictive factors

- Wound should be cleaned with soap and running water and apply direct pressure to the site of bleeding to minimize blood loss.
- Cardiopulmonary monitoring.
- Sedatives such as diazepam (Valium) to control muscle spasms.
- Antibiotics (penicillin, metronidazole) to kill the bacteria.
- Human tetanus immunoglobulin (TIG) or anti-tetanus serum should be given.
- Tetanus booster dose, if necessary.
- ***Complications***
 - Fracture of bones
 - Dislocation of joints
 - Facial palsy

Syphilis

(Synonym: Lues)
Syphilis is an infectious venereal disease caused by a spirochaete *Treponema pallidum*.

Microorganisms

- *T. pallidum* is a fragile spiral bacterium 10–15 μm long and 0.25 μm in diameter.
- It is a gram-positive, motile, microaerophilic microorganism.
- Its small size makes it invisible on light microscopy; therefore, it must be identified by its silver impregnation, immunofluorescent technique or dark field microscopy.

Mode of transmission

- Sexual contact with infectious person.
- Person like dentist working on infected patient in a contagious stage.
- Transplacental transmission, i.e. from mother to fetus in utero.
- Infected blood transfusion (organism may survive up to 5 days in refrigerated blood).
- Breaks in the skin that come into contact with infectious lesions.

Pathogenesis

- *T. pallidum* penetrates into the intact mucous membranes or microscopic dermal abrasions.
- Within a few hours, it enters the lymphatics and blood to produce systemic infection.
- Incubation time of this disease is 3 weeks but it can range from 3 days to 3 months.

Stages of development

Syphilis is usually classified as follows:

- *Acquired syphilis:* It manifests in three stages:
 1. Primary
 2. Secondary
 3. Tertiary
- *Congenital syphilis*

Clinical features

Primary syphilis

- It begins as a painless papule which may be single or multiple, with 5 mm to several centimetres in size and later it leads to an ulcer.
- Development of the primary lesion occurs after 3 weeks at the site of transmission after initial exposure. This primary lesion is called as *chancre*.
- Chancre is a painless ulcer showing dark pink colour with erythematous margin, punched-out base, raised indurated rolled edges with a button-like consistency and nonbleeding.
- Lesion may be seen in the genital organs (glans penis in males and vulva or cervix in females) and other extragenital organs such as fingers, lips,

tongue, palate, gingiva, tonsils and oropharynx.
- Enlargement and nontenderness of regional lymph nodes are seen.
- Lesions usually heal within 4–6 weeks but lymphadenopathy may persist for months.

Secondary syphilis

- Secondary syphilis develops about 4–10 weeks after the appearance of the primary lesion.
- During this stage, the spirochaetes multiply and spread entire body and may involve the palms, soles and oral mucosa.
- *Systemic symptoms:* Painless lymphadenopathy, sore throat, malaise, headache, weight loss, fever and musculoskeletal pain.
- *Mucocutaneous lesions*
 - Mucocutaneous lesions may manifest as macular, pustular, papule, papulosquamous, annular or scaling.
 - Macules are round, discrete, nonpruritic, symmetric, reddish brown in colour, 5 mm or smaller in diameter and distributed on the trunk and proximal extremities.
 - Focal area of painless, smooth, silvery grey erosions with erythematous margin is seen. These lesions undergo necrosis with slough and referred as *mucous patches.* It is found on the palate, tongue, buccal mucous and tonsils.
 - Coalescence of these mucous patches gives rise to *snail track ulcer.*
 - *Split papule* is double papules which occur at the skin fold and commissure of lip which are highly infectious.
 - *Condylomata lata* is painless, papillary lesion, which commonly develops in warm, moist sites, e.g. vulva, scrotum, inner thigh and axilla.
- Alopecia is characterized by patchy hair loss of the scalp and facial hair, including the eyebrows. This finding has been referred to as *moth-eaten appearance*.
- *Leus maligna* characterized by fever, headache and muscle pain followed by necrotic ulceration involving the face and the scalp.
- Other manifestations include malaise, arthralgias and weight loss.
- Generalized, painless lymph node enlargement is seen.
- Lesion heals eventually within 3–12 weeks, but exacerbations may occur during months or several years.
- After secondary syphilis, the patient enters a period free of lesions and symptoms known as *latent stage of syphilis*. This period of latency may last

from 1 to 30 years; then the third stage of syphilis or tertiary syphilis develops.

Tertiary syphilis

- It manifests as *gumma, cardiovascular syphilis, neurosyphilitic disease* and *ocular lesions*.
- *Gumma is a scattered active foci of granulomatous inflammation in skin, oral mucosa, upper respiratory tract, stomach, liver and larynx. It appears as a indurated nodular or ulcerated lesion that may produce extensive tissue destruction and varying size from millimetres to several centimetres in diameter.*
- *Cardiovascular syphilis* is a rare form and appears after 20 or more years of the infection. The most common manifestations are aortitis, aortic aneurysm, aortic valvulitis with regurgitation and stenosis of the coronary ostia.
- *Neurosyphilitic disease* manifests as tabes dorsalis, general paresis, psychosis, dementia, paresis and death.
- *Ocular lesions:* Iritis, chorioretinitis and Argyll–Robertson pupil (fails to react to light but responds to accommodation).
- *Oral manifestations*
 - Site: Tongue and palate.
 - Palate involvement: It begins as small, pale, raised nodular mass, which may ulcerate and progress to necrosis and perforation.
 - Tongue involvement: Diffusely with gummata and appear large lobulated and irregular shaped—*interstitial glossitis,* due to contracture of lingual musculature after healing of gammas.
 - Diffuse atrophy and loss of dorsal tongue papillae—*luetic glossitis.*

Congenital syphilis

- Transmission of infection from mother to fetus across the placenta during any stage of pregnancy and usually disease develops after 4 months of gestation.
- One-third of the cases undergo abortion, whereas one-third of the children will be normal, but one-third of the cases show congenital syphilis.
- It includes:
 - Bone and teeth deformities (stigmata of congenital syphilis)
 - Saddle nose (due to destruction of the nasal septum)

- Saber shins (due to inflammation and bowing of the tibia)
- Clutton's joints (due to inflammation of the knee joints)
- Hutchinson's triad: *Hypoplasia of incisor and molar, interstitial keratosis,* and *eighth nerve deafness*.
- Hutchinson teeth (in which the upper incisors are widely spaced and notched; appear as screwdriver-shaped)
- Interstitial keratosis (opacified cornea with loss of vision)
- Mulberry molars or Fournier's molar or moon's molar (in which the molars have agglomerated cusps)
- Higoumenakis sign (unilateral enlargement of sternoclavicular portion of clavicle)
- Mental retardation
- Rhagades (linear scar at the angle of the mouth)
- Frontal bossae
- Short maxilla with high arch palate and protuberance of mandible

Histopathology

- Both primary and secondary lesions reveal the same features except the surface epithelium. Surface epithelium of the primary lesion is usually ulcerated whereas in secondary syphilis, ulceration may not be present and epithelium demonstrates hyperplasia with spongiosis and exocytosis.
- The connective tissue is characterized by numerous plasma cells, macrophages, lymphocytes and granulation tissue. Obliterative endarteritis is characterized by the perivascular infiltration of inflammatory cells, endothelial cell proliferation and obliteration of blood vessel.
- Tertiary lesion exhibits the surface ulceration with peripheral pseudoepitheliomatous hyperplasia. Focal collection granulomatous inflammation with macrophages and multinucleated giant cells are present in the connective tissue.
- Special silver impregnation techniques like Warthin–Starry or Steiner stains or immunoperoxidase reactions directed against the organism often show scattered corkscrew-like spirochaetal organisms in surface epithelium.

Diagnosis

- Demonstration of *T. pallidum* by dark field examination.
- Nonspecific and not highly sensitive serologic screening tests:

 - Venereal disease research laboratory (VDRL) test
 - Rapid plasma reagin (RPR)
- Specific and highly sensitive tests:
 - Fluorescent treponemal antibody absorption (FTA-ABS) test
 - *T. pallidum* haemagglutination assay (TPHA)
 - *T. pallidum* particle agglutination assay (TPPA)
 - Microhaemagglutination assay for antibody to *T. pallidum* (MHA-TP)

Prognosis and predictive factors

- Primary, secondary and early latent syphilis: Single parental long-lasting penicillin G is the drug of choice.
- Late latent and tertiary syphilis: Intramuscular penicillin is administrated weekly for 3 weeks.
- Erythromycin or doxycycline or tetracycline is given, if the patient is allergic to penicillin.
- *Jarisch–Herxheimer reaction* is a process which occurs in primary or secondary syphilitic patients. This reaction occurs due to release of endotoxin when antibiotic kills large number of organisms. The clinical manifestations are mild fever, malaise, headache and skin/mucosal lesions. These signs and symptoms are temporary and fade easily.
- ***Complications:*** Carcinomatous transformation, e.g. epidermoid carcinoma.

Gonorrhoea

Gonorrhoea is a common sexually transmitted infection (STI) caused by the bacteria *Neisseria gonorrhoeae*.

Mode of transmission

- The infection can be spread by contact with the mouth, vagina, penis or anus.
- Incubation period is 1–5 days.

Clinical features

- **Age.** 15–29 years.
- **Sex.** No sex predilection.
- **Signs and symptoms**

- It usually appears 2–5 days after infection, whereas few individuals do not show any symptoms.
- Burning sensation and pain is present while urinating.
- Discharge from the penis or vagina (white, yellow or green in colour).
- Red or swollen opening of penis (urethra).
- Tender or swollen testicles.
- Sore throat (gonococcal pharyngitis).
- Severe pain in lower abdomen.
- Fever, rash and arthritis-like symptoms may occur.
- *Oral manifestations*
 - Painful ulceration on lips.
 - Gingiva may become erythematous with or without necrosis.
 - Tongue may show dry painful ulceration or swollen with painful erosion.
 - Regional lymphadenopathy.
 - Tonsillitis and pharyngitis.
 - Parotitis.

Diagnosis

- Gram stain
- Cultures of throat swab, urethral discharge, blood and joint fluid
- PCR tests

Prognosis and predictive factors

- Antibiotic and other preventive measures are taken.
- ***Complications***
 - Epididymitis
 - Salpingitis
 - Pelvic inflammatory disease
 - Infertility
 - Arthralgia

Granuloma inguinale

(Synonyms: Granuloma venereum; donovanosis)

Granuloma inguinale is a chronic bacterial infection, associated with other sexually transmitted diseases. It is caused by *Donovania granulomatis* or *Klebsiella granulomatis* or *Calymmatobacterium granulomatis*. The intracellular

organism responsible for granuloma inguinale was initially described by Donovan. Granuloma inguinale is characterized by intracellular inclusions in macrophages referred to as *Donovan bodies*.

Mode of transmission

- Primarily occurs through sexual contact.
- It may occur through the fecal route or by passage through an infected birth canal.

Clinical features

- **Age.** 20–40 years.
- **Sex.** No sexual predominance.
- **Location.** Skin and mucous membranes in the genital and extragenital regions.
- **Signs and symptoms:** Four main types of cutaneous lesions are seen:
 1. Initially, the lesion is a papule or nodule that arises at the site of inoculation. The nodule is soft, often pruritic and erythematous, and eventually ulcerates. The ulcers progressively expand and are locally destructive.
 2. Ulcerovegetative (most common): These granuloma inguinale lesions develop from nodular lesions and consist of large, usually painless, expanding, suppurative ulcers. The ulcers have clean, friable bases with distinct, raised, rolled margins and have a tendency to bleed easily and emit a putrid odour.
 3. Cicatricial: Dry ulcers evolve into cicatricial plaques and may be associated with lymphedema.
 4. Hypertrophic or verrucous (relatively rare): This proliferative reaction, with the formation of large vegetating masses.
- *Oral manifestations*
 - *Site:* Lips, buccal mucosa and palate.
 - Three types of clinical appearance like ulcerative, exuberant and cicatricial are seen.
 - It may be painful, sometimes bleeding may occur.
 - Fibrous scar may be seen.

Histopathology

- Acanthosis at the ulcer edge, with pseudoepitheliomatous hyperplasia

variably present.
- A dense dermal infiltrate of histiocytes and plasma cells is present with a scattering of small neutrophilic abscesses.
- The macrophages are large and vacuolated, and contain intracellular bacilli (i.e. Donovan bodies).
- Donovan bodies are tiny, elongated, basophilic and argyrophilic rods present within macrophages.

Diagnosis

- *Cytological smear:* Organisms are seen within the cytoplasm of histiocytes. Characteristically, they exhibit bipolar staining, which is safety-pin appearance, and are referred to as Donovan bodies. Wright–Giemsa, Warthin–Starry, toluidine blue and Leishman stains may be used to demonstrate the Donovan bodies.
- Polymerase chain reaction (PCR) techniques.
- Indirect immunofluorescent.
- Culture of *Klebsiella granulomatis*.
- If bony involvement is suspected, then radiography or other imaging studies are indicated.

Prognosis and predictive factors

- Antibiotics like trimethoprim or sulphamethoxazole and doxycycline. Alternatives include ciprofloxacin, erythromycin and azithromycin.
- Once the granuloma inguinale is healed, disfiguring genital swellings may need to be surgically corrected.

Noma

(Synonyms: Cancrum oris; gangrenous stomatitis)

Noma is derived from the Greek word *nomein*, which means *to devour*. It is a rapidly progressive, polymicrobial, opportunistic infection caused by components of normal oral flora that become pathogenic during periods of compromised immune status. Initially, it will be affected by Vincent's organism, further it is invaded by other microbes like streptococci, staphylococci and diphtheria bacilli.

Pathogenesis

- The exact cause is unknown.
- Predisposing factors
 - Malnourishment (kwashiorkor, marasmus) or dehydration
 - Major diseases like diphtheria, typhoid, measles, syphilis, leukaemia, tuberculosis, whooping cough, kala-azar, cancer (malignancy), anaemia, etc.
 - Poor sanitation and poor oral hygiene
 - Immunodeficiency disorder like AIDS
 - Unsafe drinking water and poor livelihood
- Because of these factors, the opportunistic bacterial organisms like *Borrelia vincentii* and *Fusobacterium* multiply and cause multiple ulcers, later destruction of tissue.

Clinical features

- **Age.** Children.
- **Sex.** No sex predilection.
- **Signs and symptoms**
 - It most often occurs in severely malnourished children.
 - It begins as necrotizing ulcerative gingivitis (NUG), as the disease progresses, it causes sudden, rapid tissue destruction of jaw, lips and cheek resulting in gangrenous necrosis—*necrotizing ulcerative mucositis.*
 - Overlying skin becomes inflamed, oedematous, later it may lead to necrosis with slough out tissue and sometimes, jaw may be exposed for osteomyelitis to occur.
 - Commencement of gangrene is denoted by appearance of blackening of the skin.
 - Unlike other infections, the process does not follow tissue planes and tends to spread through anatomic barriers such as muscles.
 - Subcutaneous fat pad undergo necrosis in advance of other adjoining tissues.
 - Foul odour arising from gangrenous tissue.
 - Loss of teeth is common.
 - High fever, malaise, tachycardia, increased respiratory rate, regional lymphadenopathy are seen.
 - Death may occur due to toxaemia or pneumonia.
 - Intrauterine growth retardation and premature birth may predispose to noma—*noma* neonatorum.

Prognosis and predictive factors

- Antibiotics: Penicillin and metronidazole.
- Proper nutrition is advised.
- Plastic surgery will improve facial appearance and the function of the mouth and jaw.
- Conservative debridement of gross necrotic areas is recommended but aggressive removal is contraindicated because it does not stop the extension process and compounds reconstruction problem.
- ***Complications***
 - Disfigurement
 - Discomfort, e.g. difficulty in eating, drinking and speaking

Cat scratch disease

(Synonyms: Cat scratch fever; bartonellosis)
Cat scratch disease is a bacterial infection that is caused by *Bartonella henselae.*

Pathogenesis

- Aetiology: Scratch, lick or bite of a cat.
- Cat scratch disease is not contagious from person to person.
- The bacteria transmitted, if the animal's saliva comes in contact with an eye or through broken skin.
- It usually takes 3–10 days for a blister or small bump to appear, lymph node swelling begins about 1–4 weeks later. The lesion takes 1–3 weeks to heal and swollen lymph nodes disappear within 2–4 months.

Clinical features

- **Age.** Young adults.
- **Sex.** Female predilection.
- **Location.** Arms and hands, head or scalp.
- **Signs and symptoms**
 - Fever, fatigue, loss of appetite, headache, rash, sore throat, loss of appetite and weight loss are seen.
 - A papule or pustule develops within several days after the scratch or bite. These lesions are generally not painful.
 - Regional lymph nodes become soft, fluctuant, owing to necrosis and

suppuration; later it may perforate and drain the pus.
- Parotid swelling may lead to temporary facial paralysis.
- Eye infection (irreversible retinitis, conjunctival granuloma).
- Splenomegaly and pleural effusion.

Histopathology

- Area of suppurative necrosis surrounded by the epitheloid histocyte and lymphocyte in the lymph node.
- Some cases do not show the necrosis, but there is proliferation of plumped vascular channels.
- As the disease progresses, necrosis increases and organisms become more difficult to identify.
- Special stains, such as *Warthin–Starry staining method* or *Brown–Hopps staining method,* demonstrate organisms in areas without necrosis.

Prognosis and predictive factors

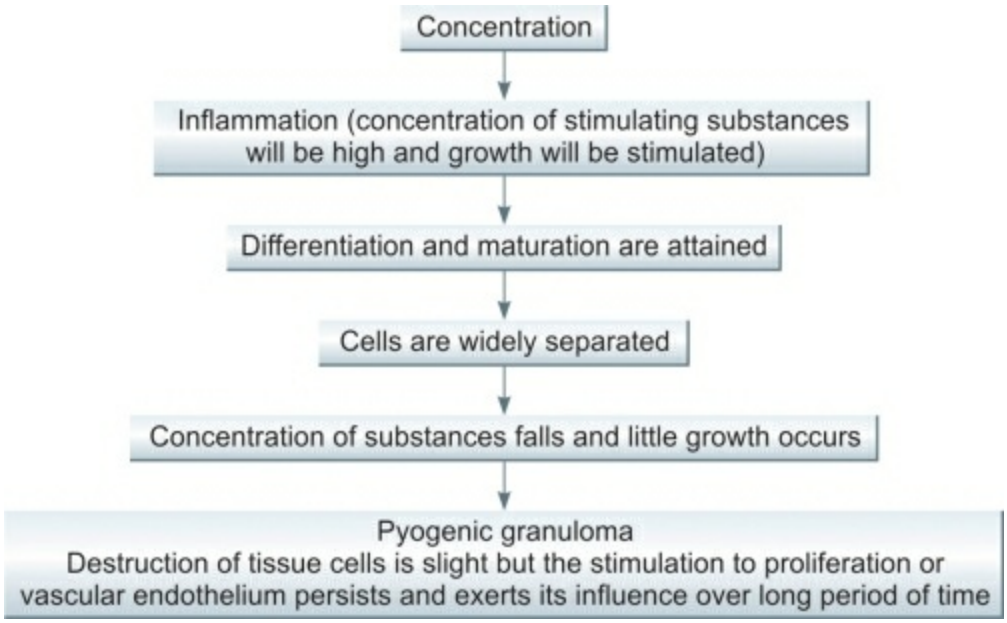
- Most cases of cat scratch disease resolve without any treatment.
- Drainage of a swollen, painful lymph node, if necessary.
- Antibiotic therapy is given.
- ***Complications***
 - Encephalopathy
 - Neuroretinitis
 - Osteomyelitis
 - Parinaud's syndrome

Pyogenic granuloma

The name *pyogenic granuloma* is a misnomer since the condition is not associated with pus and does not represent a granuloma histologically. It is a benign, highly vascular variant of capillary haemangioma. The pyogenic granuloma is a relatively common, non-neoplastic, exuberant tissue response to localized irritation or trauma.

Pathogenesis

The pathogenesis of pyogenic granuloma is illustrated in Flowchart 6.2.



FLOWCHART 6.2 Pathogenesis of pyogenic granuloma

Predisposing factors

- Idiopathic
- Trauma
- Poor oral hygiene
- Hormonal stimulation
- Chronic oral irritants (e.g. overhanging restorations, calculus)

Clinical features

- **Age.** Any age, but they most frequently affect young adults.
- **Sex.** Female predilection.
- **Location.** Gingiva, lips, tongue (especially the dorsal surface) and buccal mucosa.
- **Signs and symptoms**
 - Females are far more susceptible than males because of the hormonal changes that occur in women during puberty, pregnancy and menopause.
 - Lesion that appears on the gingiva of the pregnant women is called a *pregnancy tumour* or *granuloma gravidarum* and does occur due to hormonal changes.
 - It develops during first trimester and increases up through the 7th month of pregnancy.
 - The gradual rise in development of these lesions throughout

pregnancy is due to increased oestrogen and progesterone as pregnancy progresses.
 - After pregnancy, hormonal level returns to normal and pyogenic granuloma resolves without treatment or undergoes fibrous maturation.
 - If lesion is surgically removed during pregnancy then it usually recurs.
- The maxillary gingiva (especially in the anterior region) is involved more frequently than the mandibular gingiva; the facial gingiva is involved more than the lingual gingiva.
- Pyogenic granuloma is usually painless and represents as either pedunculated or sessile with rapid growth pattern.
- It varies in size from a few millimetres to several centimetres, and red to purple in colour.
- These tumours are soft to palpation, moist, glistening surface, sometimes, surface usually is ulcerated.
- Early lesions bleed easily due to extreme vascularity and soft in consistency.
- As lesions mature, the vascularity decreases and the clinical appearance is more collagenous and rubbery in consistency.

Histopathology (fig. 6.3)

- The epithelium overlying the lesion is flattened, atrophic or ulcerated, but the adjacent epithelium is hyperkeratotic or acanthotic.
- The ulcerated epithelium is often covered with fibrinopurulent membrane.
- The basic lesion is a lobular (cellular) haemangioma set in a fibromyxoid matrix.
- Abundant proliferation of vascular channels with endothelial cells that are engorged with red blood cells is seen.
- Scattered mixed inflammatory cells such as neutrophils, lymphocyte and plasma cells are seen.
- Mature lesions may have more collagen fibre bundles with fibroblasts.

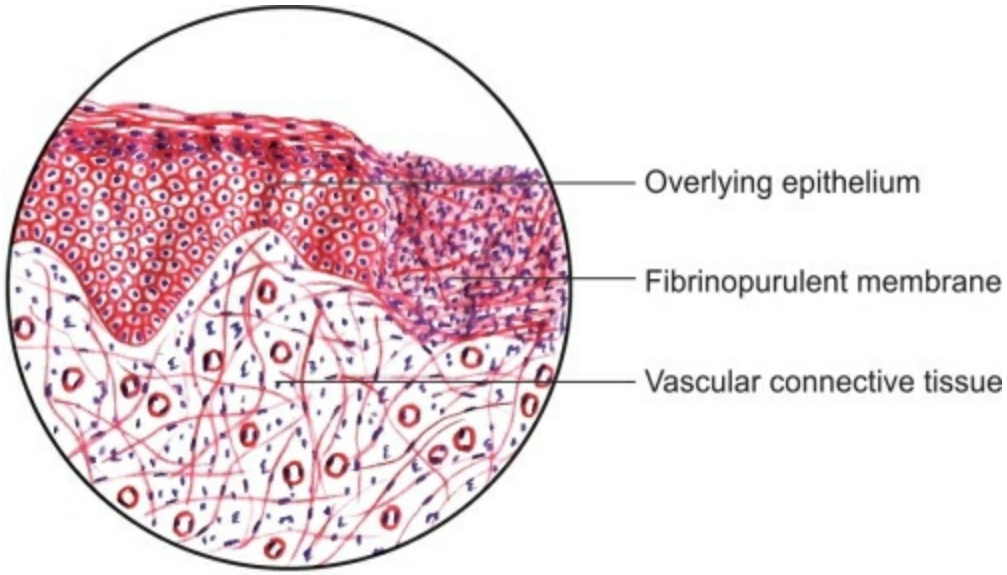


FIG. 6.3 Pyogenic granuloma.

Differential diagnosis

- Peripheral ossifying fibroma
- Peripheral giant cell granuloma
- Well-differentiated angiosarcoma

Prognosis and predictive factors

- Remove the aetiology.
- Surgical excision of the lesion.
- In case of pregnant women, the lesion may regress after the delivery, but if it persists even after delivery, surgical excision is the choice.
- Surgical removal of the lesion is not recommended during pregnancy, because of greater tendency for recurrence.

Recurrent disease may persist as a solitary nodule or as multiple small satellite nodules around the site of original lesion—*satellitosis.*

In contrast to original tumours, the satellites are usually not pedunculated, rather, are sessile and have intact surface epithelium.

Viral infections

Classification of virus groups and virus diseases

RNA viruses

- Orthomyxovirus
 - Influenza
- Paramyxovirus
 - Measles (rubeola)
 - Mumps
- Rhabdovirus
 - Rabies
 - Haemorrhagic fever
- Arenavirus
 - Lymphocytic choriomeningitis
 - Lassa fever
- Calicivirus
- Coronavirus
 - Upper respiratory infection
- Bunyavirus
- Picornavirus
 - Poliomyelitis
 - Coxsackie diseases
 - Common cold
 - Foot and mouth disease
 - Encephalomyocarditis
 - Reovirus
- Togavirus
 - Rubeola
 - Yellow fever
 - St Louis encephalitis
 - Retrovirus

DNA viruses

- Herpes virus
 - HSV-1: Gingivostomatitis, keratoconjunctivitis, genital and skin lesions

 - HSV-2: Genital and skin lesions, keratoconjunctivitis, neonatal infections and meningitis
 - Varicella-zoster virus: Varicella (chickenpox)
 - Cytomegalovirus: Cytomegalic inclusion disease
 - Epstein–Barr virus: Infectious mononucleosis, hepatitis, encephalitis
 - HSV-6: Otitis media, encephalitis
 - HSV-7: Roseola infantum
 - HSV-8: Kaposi's sarcoma, Castleman's disease
 - Simian herpes virus: Mucocutaneous lesions, encephalitis
- Poxvirus
 - Smallpox
 - Molluscum contagiosum
- Adenovirus
 - Pharyngoconjunctival fever
 - Epidemic keratoconjunctivitis
- Parvovirus
- Iridovirus
- Papovavirus
 - Human warts or papilloma
 - Tumourigenic viruses in animals

Herpes simplex infections

(Synonyms: Acute herpetic gingivostomatitis; herpes labialis; fever blister; cold sore)

- *Herpes* is derived from the Greek word *herpein*, which means *to creep* or *crawl*.
- It is the most common acute viral infectious disease affecting humans.
- It is caused by the herpes simplex virus, often referred to as *herpes virus hominis*.
- Herpes simplex virus (HSV) belongs to the family Herpesviridae and subfamily Alphaherpesvirinae.

Microorganisms

- It is composed of double-stranded DNA, protein capsid, tegument and lipid envelope, which contain glycoproteins derived from the nuclear membrane of the host cells.
- There are two types of HSV:

- HSV-1 is traditionally associated with orofacial disease.
- HSV-2 is traditionally associated with genital disease.

Pathogenesis

- **Aetiology**
 - HSV is transmitted via close personal contact and sharing the objects.
 - HSV infection occurs via inoculation of virus into susceptible mucosal surfaces (e.g. oropharynx, cervix and conjunctiva) or through small cracks in the skin.
 - The virus survives for 2–4 hours on skin and object such as cloth or plastic.
 - HSV-1 is transmitted chiefly by contact with infected saliva, whereas HSV-2 is transmitted sexually or from a mother's genital tract infection to newborn.
- **Primary infection:** The virus enters the skin or mucous membrane, usually through small cracks or breaks, and then reproduces. During this stage, oral sores and other symptoms, such as fever, may develop. The virus may not cause any symptoms, i.e. *asymptomatic infection.* It commonly occurs in children.
- **Latency:** From the infected site, the virus moves to a mass of nerve tissue in the spine called the *dorsal root ganglion*. In ganglia, the virus replicates and reproduces again, usually without any symptoms, and becomes inactive. The usual ganglia involved are trigeminal for HSV-1 and lumbosacral for HSV-2.
- **Recurrence:** The stimuli may be stress, ultraviolet light (including sunshine), fever, fatigue, hormonal changes (e.g. menstruation), immune depression and trauma to a site, where the virus may reactivate and cause new sores and symptoms. Reactivation is more common and severe in immunocompromised individuals.
- These viruses multiply in the human cells and alter their nuclei (enlarged and lobulated or multinucleated and alter their structure). HSV particles rupture the human cell's membrane as they break out of the cell.
- The incubation period is 1–26 days and occurs throughout the year.
- Both humoral and cell-mediated immunities are responsible for HSV infection.

Types of infection

- **Primary infection:** *In* persons who do not have circulating antibodies

against herpes virus.
- **Recurrent or secondary infection:** In persons who have antibodies against herpes virus.

Clinical features

- **Age.** Any age.
- **Sex**
 - HSV-1: No sex predilection.
 - HSV-2: Female predilection.
- **Signs and symptoms**
 - Up to 80% of herpes simplex infections are asymptomatic.
 - HSV-1 infections are more common in children but primary herpes gingivostomatitis can be seen at any age. HSV-2 infections are seen among adults (primarily after the onset sexual activity) and newborn baby from a maternal episode at delivery time.
 - The clinical course of HSV infection depends on the age and immune status of the host, the anatomic site of involvement and the antigenic virus type.
- **Herpes genitalis**
 - Herpes genitalis can be caused by HSV-2.
 - Site: Uterine cervix, vagina, vulva and penis.
 - Transmitted through sexual contact.
 - In recent years, HSV-1 on the genitalia and HSV-2 on the oral mucous membrane are seen due to changing sexual practice in recent years.
- **Herpetic meningoencephalitis**
 - Sudden fever and increased intracranial pressure
 - Convulsion, and paralysis of muscle
- **Herpetic conjunctivitis**
 - Swelling and congestion of the palpebral conjunctiva
 - Keratitis
 - Corneal ulceration
 - Herpetic vesicle of the eyelid
- **Herpetic eczema**
 - Diffuse vesicular lesion of the skin.
 - It is of extremely serious nature.
 - It may superimposed on sever seborrhoeic dermatitis, impetigo, scabies, Darier disease and pemphigus vulgaris.
- **Disseminated herpes simplex of the newborn**

- If the mother is affected with herpetic vulvovaginitis, the newborn baby acquires the infection during birth.
- Infants usually manifest the disease by the 4th to 7th days of life and die on the 9th to 12th days of life.

- **Herpetic whitlow:** It occurs in nail due to autoinoculation.
- **Herpes gladiatorum:** It occurs among wrestlers.
- **Primary herpetic stomatitis**
 - It is transmitted by droplet spread or contact with lesions.
 - Age: It affects children and young adults.
 - Site: Gingival, lips, tongue, buccal mucosa, palate, pharynx and tonsils.
 - Fever, irritability, headache, pain upon swallowing and regional lymphadenopathy are seen.
 - Mucosa becomes painful, erythematous and oedematous.
 - Yellowish, fluid-filled vesicle which ruptures and form shallow, ragged and painful ulcer covered by grey membrane and erythematous halo.
 - Ulcers may vary in size, measuring several millimetres to centimetres in diameter and heals within 7–14 days without scarring.
 - Lymph nodes often enlarge and become painful.
- **Secondary or recurrent herpetic labialis/stomatitis or recrudescent herpes infection**
 - Age: Any age.
 - Site: Hands, fingers, eyes, lips, hard palate and attached gingiva.
 - It occurs due to some stimuli like stress, ultraviolet light (including sunshine), fever, fatigue, hormonal changes (e.g. menstruation), immune depression and trauma.
 - Pain, burning and tingling sensation often occur at the lip, followed by the development of tiny, thin-walled, intraepidermal vesicles that become pustular and later they rupture to form red ulceration with slight erythematous halo.
 - Ruptured vesicles are covered by a brownish crust.
 - Lesions heal within 7–10 days without scar formation.
 - Regional lymphadenopathy.

Histopathology

- Infected cells are swollen and have pale eosinophilic cytoplasm and large vesicular nuclei, which are called as *ballooning degeneration.*
- Epithelial cells contain eosinophilic intranuclear inclusion bodies known as *lipschutz* bodies. These bodies are eosinophilic, ovoid, homogenous

structure within the nucleus which tend to displace the nucleolus and nuclear chromatin peripherally and produce the peri-inclusion halo.
- Multinucleated giant cells are seen.
- Inflammatory cell infiltrate is common.
- The ulcerated area is covered by the exudates, fibrin, PMN and degenerated cells.

Diagnosis

- Isolation of the virus in tissue culture
- Immunofluorescent staining of the tissue culture cells and smears
- Immunoperoxidase technique
- Punch biopsy
- Detection of HSV-DNA with polymerase chain reaction (PCR) techniques
- Serologic tests such as complement fixation assay, radioimmunoassay and ELISA
- *Tzanck test*
 - Typically, an intact vesicle is used from which the vesicular fluid is aspirated by puncture with a sterile tuberculin syringe.
 - Using a sterile instrument, the floor of the newly produced ulcer can then be scrapped. The obtained material can be spread on a glass microscope slide and then dried and fixed for staining.
 - Staining can be performed with a Papanicolaou or Giemsa or Wright stain.
 - A positive result is the finding of Tzanck cells.

Differential diagnosis

- Chancroid
- Hand–foot–mouth disease
- Herpes zoster

Prognosis and predictive factors

- A topical anaesthetic such as lidocaine (dilocaine, nervocaine, xylocaine, zilactin-L) may be prescribed to relieve pain.
- Administration of antiviral drugs includes acyclovir, idoxuridine and vidarabine.
- Antibiotic therapy helps in the prevention of secondary infection.

Herpes zoster infections

- Varicella-zoster virus (VZV) is the agent causing *varicella* or *chickenpox*, the common childhood infection.
- Following resolution of chickenpox, VZV lies dormant in the spinal dorsal root ganglia until a decrease in cellular immunity triggers the reactivation of the virus, resulting in *herpes zoster* or *shingles.*
- VZV is a double-stranded DNA virus belonging to the Herpesviridae family.

Chickenpox

(Synonym: Varicella)

Chicken pox is an acute, contagious viral disease caused by VZV.

Mode of transmission

Microorganism enters the respiratory system through air-borne droplet or direct contact with infected lesion.

Clinical features

- **Age.** 5–9 years.
- **Sex.** No sex predilection.
- **Location.** Trunk, face and extremities.
- **Signs and symptoms**
 - It occurs commonly in the winter and spring months.
 - *Skin lesions*
 - Initially, the lesions appear at unilateral side and turns to vesicles in 1–2 days. Sometimes coalescing to form bullae. The lesions then rupture and release their contents, ulcerate, and forms crust over it.
 - Scarring and hyperpigmentation or hypopigmentation at lesion sites may persist for a long period or may remain permanently.
 - The lesion begins on the trunk and spread to face and extremities.
 - Pain will be constant, severe and burning, throbbing or stabbing in nature. Pain duration is variable but it occurs usually less than 1 month.
 - Systemic symptoms such as headache, low-grade fever, malaise, fatigue or anorexia.
 - Corneal ulcers and conjunctivitis are seen.
 - Regional lymphadenopathy.

- *Oral manifestations*
 - Site: Buccal mucosa, tongue, gingiva, palate and mucosa of the pharynx.
 - Mucosal lesions: Initially, slightly raised vesicle with surrounded erythema is seen. Later, it ruptures soon and form an ulcer.
 - Loss of taste in the anterior portion of tongue is seen.

Histopathology

- Similar to HSV.
- The VZV causes acantholysis with formation of numerous free-floating *Tzank cells,* which exhibits nuclear margination of chromatin and occasional multinucleation.

Complications

- **In children:** Reye's syndrome, secondary skin infection, encephalitis, cerebellar ataxia, pneumonia, GI disturbances like vomiting, diarrhoea and haematologic events, e.g. thrombocytopaenia, pancytopaenia, haemolytic anaemia and sickle cell anaemia.
- **In adults:** Varicella pneumonitis, encephalitis, ataxia, headaches, drowsiness, convulsions or coma. The risk of death is greater in adults because of increased prevalence of encephalitis.
- **In pregnancy:** Congenital or neonatal chickenpox, abortion or congenital defects.
- **In immunocompromised patients:** High fever, hepatitis, pneumonitis, pancreatitis, GI obstruction and encephalitis.

Herpes zoster

(Synonym: Shingles)
Herpes zoster is an acute infectious viral disease caused by VZV.

Pathogenesis

- In humans, primary infection with VZV occurs when the virus comes into direct contact with the mucosa of the respiratory tract or conjunctiva. Later, it is distributed throughout the body via mononuclear cells in the bloodstream.
- After primary infection, the virus migrates along sensory nerve fibre to the satellite cells of dorsal root ganglia where it becomes dormant. This

dormant virus may reactivate due to decreased cellular immunity, and results in herpes zoster.

- The triggering factors include trauma, tumour, local X-ray radiation and immunosuppressive drugs lead to reactivation of VZV.
- Herpes zoster results from the reactivation of VZV in the trigeminal (5th cranial) nerve. Any branch of the nerve may be affected, but the first division of the trigeminal nerve is most commonly involved.
- VZV reactivation causes inflammation in the dorsal root ganglion, accompanied by haemorrhagic necrosis of nerve cells, which results in neuronal loss and fibrosis.
- The distribution of the rash corresponds to the sensory fields of the infected neurons within a specific ganglion.
- The incubation period is 1–2 weeks.

Clinical features

- **Age.** Adults. The incidence of herpes zoster increases with age.
- **Sex.** No sex predilection.
- **Location.** Trunk, face and extremities.
- **Signs and symptoms:** It is grouped into three phases—*prodrome, acute* and *chronic phases*.

1. Prodromal phase

- Prodromal signs and symptoms develop 1–4 days before cutaneous or mucosal lesions.
- Pain, fever, malaise, headache and migraine are commonly seen.
- Initial viral replication—ganglionitis—neuronal necrosis and neuralgia.
- As the virus travels down the nerve, the pain intensifies as burning, tingling, itching, boring, prickly or knife-like nature.
- The pain develops in the area of epithelium innervated by affected sensory nerves.
- There may be recurrence in the absence of vesiculation of skin or mucosa —*zoster sine herpete* (zoster without rash). Severe pain of abrupt onset, hyperaesthesia over specific dermatome, fever, headache, myalgia and lymphadenopathy are seen.

2. Acute phase

- Clusters of vesicles set on an erythematous base.
- Within 3–4 days, the vesicles become pustular and ulcerate.

- Crust develops after 7–10 days.
- Lesions follow the pain of affected nerve and terminate at the end line.
- Exanthema resolves within 2–3 weeks in healthy individuals.
- On healing, scarring with hypopigmentation or hyperpigmentation is seen.
- ***Oral manifestations***
 - Oral lesions occur with trigeminal nerve involvement on movable or bound mucosa.
 - Lesions extend to midline in conjunction with skin involvement overlying affected quadrant.
 - Lesions manifest as 1–4 mm, white, opaque vesicles that rupture to form shallow ulcerations.
 - Bone necrosis occurs with loss of teeth in areas involved with herpes zoster, because of cross-anatomic relationship between nerves and blood vessels within neurovascular bundles. Inflammatory process within nerve has potential to extend adjacent vessels.
 - *Gnathic osteonecrosis:* Secondary to damage of blood vessels supplying the alveolar ridges and teeth, leading to focal ischaemic necrosis. Interval between appearance of exanthema and osteonecrosis is 21 days.
- ***Ocular involvement***
 - Direct viral-mediated epithelial damage
 - Neuropathy
 - Secondary vasculopathy
 - Permanent blindness

Ramsay Hunt Syndrome

- It is also known as *herpes zoster oticus or geniculate neuralgia or herpes zoster auricularis.*
- Ramsay Hunt syndrome is caused by VZV reactivation involving the facial and auditory nerves.
- Vesicular eruptions may manifest anywhere in the facial nerve distribution.
- Hearing impairment, nystagmus, hoarseness, tinnitus, vertigo and pain in the external auditory meatus and pinna of the ear.
- Loss of taste sensation in the anterior two-thirds of the tongue.
- Facial paralysis.

3. Chronic phase

- 15% of affected patients progress to chronic phase.
- Pain (post-herpetic neuralgia) that persists longer than 3 months after the initial presentation of the acute rash.
- It affects patients older than 60 years of age.
- Pain: Burning, throbbing, aching, itching or stabbing caused by light stroking of area or from contact with adjacent clothing.

Histopathology

Similar to herpes simplex infection.

Diagnosis

- Cytologic smear
- Tzanck test
- Viral culture
- Serological test

Prognosis and predictive factors

- Antiviral drug administration.
- The prognosis for younger and healthy patients is excellent.
- Elderly people significantly show increased risk of complications.
- ***Complications***
 - Post-herpetic neuralgia
 - Deafness
 - Meningoencephalitis
 - Cranial nerve palsies
 - Pneumonitis

Hand–foot–mouth disease

(Synonym: Coxsackie virus infection)

- Hand–foot–mouth disease is a relatively common viral infection that usually begins in the throat.
- It is caused by *Coxsackie virus A16*, a member of the Enterovirus family.

Pathogenesis

- It can be spread by person to person, i.e. direct contact with nose and throat discharges saliva, fluid from blisters, or the stools of an infected

person.
- The incubation period is about 3–7 days.

Clinical features

- The disease usually begins with a fever, poor appetite, malaise (feeling vaguely unwell), and often with a sore throat.
- Small, flat or raised, red, tender or painful, rashes seen on hands, feet and buttocks.
- Painful sores usually develop in the mouth. They begin as small red spots that blister and then often become ulcers. The sores are usually located on the tongue, gums and inside of the cheeks.

Prognosis and predictive factors

- There is no specific treatment for the infection other than relief of symptoms.
- ***Complications***
 - Febrile seizures
 - Aseptic meningitis
 - Encephalitis

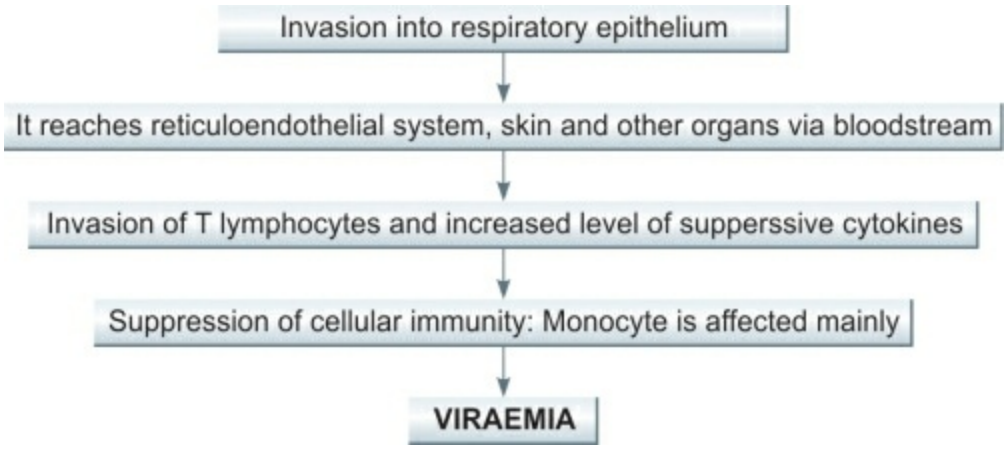
Measles

(Synonyms: Rubeola; red measles; hard measles; nine-day measles)

- Measles is a viral infection caused by a paramyxovirus.
- Paramyxovirus belongs to the family Paramyxoviridae which is an RNA virus.
- It is an acute, contagious, dermatropic viral infection.

Pathogenesis (flowchart 6.3)

- It arises in the spring season and spreads by direct contact or with respiratory droplets.
- It is mainly spread in large families, crowded people or slums.



FLOWCHART 6.3 Pathogenesis of measles

Clinical features

- Incubation period of measles is 8–12 days.
- Individuals are infected from 2 days before symptoms until 4 days after appearance of associated rash.
- Lacrimation, photophobia and conjunctivitis.
- Cough, fever, malaise, muscle pain and loss of appetite.

Stages of infection

There are three stages of infection. Each stage lasts for three days—*nine-day measles.*

First stage

- First three days.
- **3Cs**
 - *Coryza:* Running nose
 - *Cough:* Brassy and uncomfortable
 - *Conjunctivitis:* Red, watery and photophobic eyes
- Fever typically accompanies these symptoms.
- *Koplik's spots:* These are bluish white macules or greyish spots on buccal and labial mucosa. These are characterized by numerous small, bluish irregularly shaped flecks, white specks surrounded by a bright red margin. These lesions coalesce to form patches.
- Pathognomonic spots rarely noted on inner conjunctival fold of eye or vaginal mucosa. They represent foci of epithelial necrosis—*grains of salt on a red background.*

Second stage

- Fever will continue.
- Koplik's spots fade.
- Maculopapular and erythematous (morbilliform) rash begins, which tends to blanch on pressure. It involves face initially, later it spreads down to involve trunk and extremities.
- Abdominal pain secondary to lymphatics involvement is seen.

Third stage

- Fever ends.
- Rashes begin to fade and demonstrate a similar downward progression with replacement by brown pigmentary staining.
- Desquamation of skin is noted in the previously affected by rash.

Oral manifestations

- Oral lesions occur prior to the cutaneous lesions.
- Koplik's spots.
- Palatal and pharyngeal petechiae.
- Inflammation, congestion, swelling and focal ulceration of the gingiva, palate and throat.
- Severe measles affect the odontogenesis resulting in enamel hypoplasia.
- Enlargement of lymphoid tissue.

Histopathology

- Area of focal hyperparakeratosis.
- Spongiosis (intercellular oedema).
- Dyskeratosis.
- Sometimes, epithelial ulceration is seen.
- Multinucleated giant cells called *Warthin–Finkeldey giant cells* are present. In 1931, Warthin and Finkeldey reported multinucleated giant cells in hyperplastic lymphoid tissue, which is called *Warthin–Finkeldey giant cells*.

Diagnosis

- Serological antibody titre
- Viral culture

Prognosis and predictive factors

- There is no specific treatment.
- Complete bed rest.
- Vitamin A supplements
- ***Complications***
 - Encephalitis
 - Otitis media
 - Pneumonia
 - Noma
- *Prevention*
 - Routine immunization, i.e. *MMR vaccine (measles, mumps and rubeola)* is highly effective for preventing measles and recommended for all children.
 - *MMR vaccination:* 5 ml of vaccine is given subcutaneously.
 - First dose of vaccination: 9 months old.
 - Second dose of vaccination: 15–18 months old.

Rubeola

(Synonyms: Three-day measles; German measles)

- Rubeolla is a viral infection caused by the *paramyxovirus.*
- It is spread through the air or by close contact.
- The greatest importance of this infection lies not in its acute illness but in its capacity to induce birth defects in fetus.

Clinical features

- **Age.** Adults.
- **Sex.** No sex predilection.
- **Location.** Trunk, face and extremities.
- **Signs and symptoms**
 - Rubeola causes milder symptoms than measles.
 - The incubation period is 14–21 days.
 - Infected patients are contagious from 1 week before exanthema to 5 days after development of rash.
 - Prodromal symptoms are seen from 1 to 5 days before exanthema.
 - Exanthematous rash
 - Initially, it occurs on the face and moves down to the trunk.
 - The rash forms discrete pink macules, then papules and finally fades with flaky desquamation.

- The rash fades as it spreads and often exhibits facial clearing before the completion of its spread into lower body areas.
- Rash resolves completely by 3 days *(hence named three-day measles).*

- Infants with congenital infection—*congenital rubeola syndrome (CRS)*
 - Transmission: First 12 weeks of pregnancy—fetal damage; after 12 weeks of pregnancy—CRS
 - *Classic triad:* Deafness, heart disease and cataracts
- *Oral manifestations*
 - *Forchheimer's sign:* Small discrete, dark red papules that develop on soft palate and may extend on to the hard palate. This lesion arises simultaneously with rash becoming evident in 6 hours after first symptoms and not lasting longer than 12–14 hours.

(It is also seen in rubeola, roseola, infectious mononucleosis, septicaemia, scarlet fever.)

- Koplik's spots do not occur.
- Enamel hypoplasia.
- High caries incidence.
- Delayed eruption of deciduous teeth.

Prognosis and predictive factors

- There is no treatment for this disease.
- Symptomatic treatment is advised.
- Complications
 - Miscarriage or stillbirth
 - CRS
 - Encephalopathy
 - Mental retardation
- *Prevention:* Routine immunization, i.e. *MMR vaccine (measles, mumps and rubeola).*

Smallpox

(Synonym: Variola)

- Smallpox is an acute, serious and contagious disease due to a pox virus.
- It is the only disease that has been completely wiped out throughout the world.

Pathogenesis

- Smallpox spreads easily from one person to another from saliva droplets.
- On 9 December 1979, World Health Organization (WHO) declared that all countries should stop vaccinating for smallpox, so that it would not return as an endemic disease.

Clinical features

- **Age.** Children and young adults.
- The incubation period is about 7–12 days.
- Fatigue, high fever, malaise, headache and vomiting are present.
- *Skin lesions*
 - It starts as macules and papules at 48–72 hours (flat, red lesions).
 - Papule develops into vesicles (raised blisters) form, later it turns into pustules which is small, elevated and yellowish green with inflamed border.
 - Desquamation occurs at the healing phase on 12–17 days.
 - It first appears on the face and later it spread to other parts of the body.
- *Oral manifestations*
 - Development of pustule, it ruptures and forms ulceration of the oral mucosa.
 - Enlarged and painful tongue resulting in dysphagia.

Prognosis and predictive factors

- There is no drug specifically for treating smallpox.
- Sometimes, antibiotics are given for infections.
- ***Complications***
 - Arthritis
 - Encephalitis
 - Septicaemia
 - Death
- *Prevention:* Many people were vaccinated against smallpox in the past. The vaccine is no longer given now because the virus has been wiped out.

Molluscum contagiosum

Molluscum contagiosum is a viral skin infection caused by poxvirus family.

Pathogenesis

- The virus can spread through contact with contaminated objects such as towels, clothing or toys.
- The virus also spreads by sexual contact.
- More often seen among immunocompromised (AIDS) patients.

Clinical features

- **Age.** Children and young adults.
- **Sex.** Male predilection.
- **Location.** Face, neck, arms and hands but may occur anywhere on the body except the palms and soles.
- **Signs and symptoms**
 - The incubation period is 2–7 weeks.
 - *Skin lesion*
 - It begins as a numerous small, painless, red papule that may become elevated nodule.
 - The papule often has hemispheric shape with dimple in the centre which may be keratinized; it is 5 mm in diameter.
 - Lesion heals spontaneously in about 30–60 days.
 - Lack of inflammation and necrosis differentiates these lesions from other pox virus lesions.
 - *Oral manifestations*
 - Oral manifestations are not common.
 - *Site:* Lips, tongue and buccal mucosa.
 - Oral lesions are similar to skin lesion.

Histopathology

- Localized, lobular, inward proliferation of surface stratified squamous epithelium is seen.
- Central portion of each lobule is filled with bloated keratinocytes that contain large intracytoplasmic basophilic viral inclusions called *Henderson–Patterson inclusion bodies or molluscum bodies or Cowdry type A inclusion bodies.*
 - These bodies begin as small eosinophilic structures in cells just above the basal layer. As they approach the surface, these bodies increase in size.
 - These bodies measure about 25 μm in diameter.
- Central crater is formed at the surface as stratum corneum; later these cells disintegrate to release molluscum bodies.

Prognosis and predictive factors

- Treatment for molluscum contagiosum is not always mandatory. The lesions often disappear themselves and heal without scarring.
- Individual lesions may be removed surgically or electrosurgery.
- Topical application of drugs like podophyllin and cantharidin may help to resolve lesions.
- ***Complications***
 - Persistence, spread or recurrence of lesions.
 - Secondary bacterial skin infections.

Condyloma acuminatum

(Synonyms: Verruca acuminata; venereal wart)

- The human papillomavirus (HPV) was identified as the virus responsible for condyloma acuminatum.
- HPV type 6, a11, a30, b42, 43, 45 46b, 51, b54, 55, 70 can infect the anogenital tract and HPV-6 affect the oral cavity.

Mode of transmission

It is transmitted by sexual contact, close contact with infected person.

Pathogenesis

- Virus inoculates into epithelium, and replicates and transcribes in the basal cells.
- Virions are released along with desquamated epithelial cells.

Clinical features

- **Age.** 18–25 years.
- **Sex.** No sex predilection.
- **Location.** Anogenital organ and oral cavity such as buccal mucosa, palate, gingiva and alveolar ridge.
- **Signs and symptoms**
 - Typically condyloma is usually discrete, papillary, cauliflower-like lesion that involves multiple sites.
 - Soft pink nodule, which proliferates and coalesces to form diffuse papillomatous cluster.
 - Lesions are not painful, but they can be associated with pruritis.

Histopathology

- It shows evidence of hyperkeratosis, acanthosis and parakeratosis.
- Koilocytosis, which is perinuclear cytoplasmic halos, is commonly observed in the superficial spinous layer.
- A chronic inflammatory infiltrate, oedematous with dilated capillaries is often observed within the dermis.

Prognosis and predictive factors

- Medication like podophyllin, imiquimod, sinecatechins or 5-fluorouracil can be applied topically.
- Surgical removal of warts.
- Carbon dioxide laser therapy.
- Electrosurgery.
- A human papillomavirus (HPV) quadrivalent vaccine is now available for prevention of HPV-associated disease.

Mumps

(Synonym: Epidemic parotitis)

MumpMumps is an acute contagious disease that leads contagious disease that leads to painful swelling of the salivary glands. It is caused by the *paramyxovirus.*

Microorganisms

- It is a single-stranded, negative-sense RNA surrounded by an envelope.
- It is sensitive to heat and ultraviolet light.

Pathogenesis

- *Mode of transmission*
 - The virus spreads from person to person by respiratory droplets (e.g. when you sneeze) or by direct contact with items that have been contaminated with infected saliva.
 - Infants born to mothers who have mumps in the week prior to delivery.
- After the initial entry into the respiratory system, the virus replicates in the respiratory epithelium then reaches the other target tissues such as the CNS, lymph nodes and salivary glands, particularly the parotid glands and develops a viraemia.

- Salivary glands show oedema, cell necrosis and inflammation with mononuclear cell infiltration. Sometimes, focal haemorrhage and destruction of germinal epithelium may occur.

Clinical features

- **Age.** Children and young adults.
- **Sex.** No sex predilection.
- **Location.** Central nervous system, pancreas and salivary gland.
- **Signs and symptoms**
 - The incubation period is usually 12–24 days.
 - Fever, headache, sore throat, chill, vomiting and myalgia are seen.
 - Unilateral or bilateral swelling of the salivary glands (usually parotid gland) is seen.
 - Swelling of the parotid gland reaches maximum for about 2–3 days and then gradually subsides.
 - Swelling may last for 7–10 days.
 - Pain is most intense during the period of maximal enlargement. Chewing movements of jaws or eating saliva stimulation tends to increase the pain.
 - The salivary duct opening may be erythematous and oedematous in appearance.

Prognosis and predictive factors

- There is no specific treatment for mumps.
- Ice or heat packs applied to the neck area and acetaminophen (Tylenol) may help relieve pain.
- Maintain hydration and vaccination.
- ***Complications***
 - *Epididymo-orchitis*
 - *Oophoritis and mastitis*
 - *Abortion*
- *Prevention:* MMR immunization (vaccine) protects from mumps.

Human immunodeficiency virus infection (HIV)

- HIV infection or AIDS is a condition caused by the *human immunodeficiency virus (HIV).*
- The condition gradually destroys the immune system, which leads to

numerous opportunistic infections, neoplasms and neurological disorders.

- There will be severe reduction in CD4 cells, which is an important part of the immune system. These cells are often referred to as *T cells*.

Microorganisms

- HIV infection is caused by HIV-1 and HIV-2.
- HIV-1 is more common in central Africa and other parts of the world and HIV-2 in West Africa and India.
- HIV is a lentivirus group type III which belongs to the group of viruses called *retroviruses*.
- Virion is an icosahedral structure which contains external spikes formed by two major envelop proteins, the external gp120 and transmembrane gp41. The core protein p17 is found outside the viral nucleoid and forms the virion matrix. The HIV glycoreceptors attach with specific antireceptors (GP-120 and GP-41), which are typically found on T_4 lymphocytes and white blood cells (WBCs).

Mode of transmission

HIV can be spread by the following ways:

- Through sexual contact, i.e. homosexual or heterosexual, including oral, vaginal and anal sex.
- Through blood—blood transfusions, accidental needle sticks or needle sharing.
- From mother to child—a pregnant woman can transmit the virus to her fetus through their shared blood circulation or a nursing mother can pass the virus to the baby by her breast milk.

Pathogenesis

- HIV virus enters into the body and primarily affects the CD4 T lymphocyte by binding to the receptor of the T lymphocyte.
- Lentiviruses are transmitted as single-stranded, positive-sense, enveloped RNA viruses.
- Upon entry into the target cell, the single-stranded viral RNA genome is converted (reverse transcribed) into double-stranded DNA by a virally encoded reverse transcriptase by the process of reverse transcription.
- The resulting viral DNA is then imported into the cell nucleus and

integrated into the cellular DNA and synthesizes the retroviral structure protein like *nef, tat* and *rev*, etc.

- Once integrated, the virus may become latent, allowing the virus and its host cell to avoid detection by the immune system.
- Ultimately, the involved cells die and produce new RNA genomes, and viral proteins are released from the cell, further they attack some more new cells and lead to the decrease of CD4 lymphocytes in the blood.
- The normal count of CD4 T cells is 500–1500 mm^3 and the ratio of CD4 helper and CD4 suppressor cells are 2:1. This value may vary depending upon the severity of infection.

Clinical features

- The symptoms of HIV/AIDS may vary depending on the phase of infection.
- In 1990, the World Health Organization (WHO) introduced staging system for patients infected with HIV.
 - *Stage I:* HIV infection is asymptomatic and not categorized as AIDS. But HIV is infectious.
 - *Stage II:* It includes minor mucocutaneous manifestations and recurrent upper respiratory tract infections.
 - *Stage III:* It includes unexplained chronic diarrhoea for longer than a month, severe bacterial infections and pulmonary tuberculosis.
 - *Stage IV:* It includes toxoplasmosis of the brain, candidiasis of the oesophagus, trachea, bronchi or lungs and Kaposi's sarcoma.
- In 1993, revised staging system for HIV infection is introduced based on the degree of immunodeficiency:
 - *Early stage:* $CD4^+$ T cell count >500/µl
 - *Intermediate stage:* $CD4^+$ T cell count 200–500/µl
 - *Advanced stage:* $CD4^+$ T cell count <200/µl

Within the first few weeks

- Usually there are no signs or symptoms in 1–2 weeks, but after 2–4 weeks, patients may show illness.
- Signs and symptoms may include:
 - Fever
 - Headache
 - Sore throat
 - Swollen lymph nodes

- Rash on skin

Within 1–2 years

This phase shows no symptoms for years. But, as the virus continues to multiply and destroy immune cells, it may develop mild infections or chronic symptoms such as:

- Swollen lymph nodes
- Diarrhoea
- Weight loss
- Fever
- Cough and shortness of breath

After 10 years

If the patient has not received treatment for HIV infection, the disease typically progresses to AIDS in about 10 years and immune system has been severely damaged. The signs and symptoms may include:

- Night sweats
- Chills or fever higher than 100°F (38°C) for several weeks
- Cough and shortness of breath
- Chronic diarrhoea
- Persistent white spots or unusual oral lesions
- Persistent, unexplained fatigue
- Blurred and distorted vision
- Weight loss
- Skin rashes or bumps
- Persistent generalized lymphadenopathy
- Haematologic disease such as hypoproliferative anaemia and thrombocytopaenia
- Neurologic disorders such as aseptic meningitis
- Dermatologic disorders

Oral manifestations

- In 1995, WHO collaborating centre classified oral manifestations of HIV infection as follows:
 - Presumptive criteria: Related to the initial clinical appearance of lesion
 - Definitive criteria: Based on special investigation for absolute diagnosis
- In 1993, European Commission–Clearing House classification of the oral manifestation of AIDS in adults.

- *Group 1: Lesion strongly associated with HIV*
 - Candidiasis
 - Hairy leukoplakia
 - Angular cheilitis
 - Kaposi's sarcoma
 - Non-Hodgkin's lymphoma
 - Periodontal disease: Gingivitis, necrotizing ulcerative gingivitis (NUG) and necrotizing ulcerative periodontitis (NUP)
 - Cervical lymphadenopathy
- *Group 2: Lesion less commonly associated with HIV*
 - Bacterial infection: *Mycobacterium tuberculosis*
 - Melanotic hyperpigmentation
 - Necrotizing ulcerative stomatitis
 - Unilateral or bilateral enlargement of salivary gland
 - Thrombocytopaenic purpura
 - Oral ulcerations
 - Viral infection: Herpes simplex virus, human papilloma virus, varicella-zoster virus
- *Group 3: Lesion associated with HIV*
 - Bacterial infection, e.g. actinomycosis, pneumonia, cat scratch disease, herpes simplex, herpes zoster and syphilis
 - Viral infections, e.g. molluscum contagiosum, cytomegalovirus infection
 - Fungal infections, e.g. candidiasis, aspergillosis, cryptococcus, histoplasmosis, zygomycosis, toxoplasmosis
 - Neurological disorders, e.g. facial palsy and trigeminal neuralgia
 - Recurrent aphthous stomatitis
 - Dermatologic disorder, e.g. erythema multiforme, lichen planus
 - Osteomyelitis
 - Thrombocytopaenic purpura
 - Delayed wound healing

Diagnosis

- ELISA test
- Western blot tests
- To detect antibodies to the HIV in serum
- To detect the virus from peripheral blood
- A complete blood count (CBC) and white blood cell count
- Polymerase chain reaction (PCR) technique

- Ratio of helper and suppressor T lymphocytes
- Hypergammaglobulinaemia
- Viral culture
- p24 antigen detection
- Immunological test and surrogate markers
- Salivary test

Prognosis and predictive factors

- Antiretroviral treatment of acute HIV infection is controversial.
- Several studies have shown no particular antiretroviral therapy for this disease.
- *Prevention:* Currently there is no vaccine available for HIV/AIDS.

Fungal infections

Oral candidiasis

(Synonyms: Moniliasis; oral thrush)

- It was first described by the French paediatrician *Francois Valleix* in *1838.*
- Candidiasis is caused by yeast-like fungus called *Candida.*
- *Candida albicans* is the most frequent causative organism for candidiasis.
- Other species include *C. tropicalis, C. parapsilosis, C. stellatoidea, C. kruse, C. guillermondi, C. dirbliniensis and C. glabrata.*
- *Candida* is the common inhabitant of the oral cavity, vagina and gastrointestinal tract of normal person.

Microorganisms

- It exists in three forms: *pseudohyphae, yeast* and *chlamydia forms.*
- It reproduces by asexual budding and forms pseudohyphae.
- These species grow rapidly at 25–37°C.

Pathogenesis

- *C. albicans* causes thrush when normal host immunity or normal host flora is disrupted, hence it is called *opportunistic infection*.
- Invasion of organism occurs under certain circumstances.
- Salivary IgA affects the adherence of *Candida* to mucosa.
- Overgrowth of yeast on the oral mucosa leads to desquamation of epithelial cells and accumulation of bacteria, keratin, necrotic tissue and debris to form a pseudomembrane, which may closely adhere to the mucosa.
- This membrane shows extensive areas of oedema, ulceration and necrosis of the underlying mucosa.
- T cells, neutrophils, antifungal factors and anticandidal factors play a major role in the development of infection.
- *Predisposing* factors
 - Person who is taking medications, e.g. antibiotics and immunosuppressive drugs
 - Radiation therapy
 - Chronic illness
 - Systemic diseases, e.g. diabetes, anaemia, myxoedema and Addison's

disease
- Immunocompromised patients, e.g. AIDS
- Severe debilitation
- Nutritional deficiency, e.g. vitamins A and B_6, iron
- Old age or infants
- Pregnancy
- Denture wearer and smokers

Classification of oral candidiasis

Classification of oral candidiasis is described in Table 6.1.

Table 6.1

Classification of oral candidiasis *(as proposed by Samaranayake, 1991; and modified by Axell et al, 1997)*

Primary oral candidiasis	Secondary oral candidiasis
Acute forms • Pseudomembranous • Erythematous	Oral manifestations of systemic mucocutaneous candidiasis as a result of disease such as *thymic aplasia* and *candidiasis endocrinopathy syndrome*
Chronic forms • Hyperplastic: Nodular Plaque-like • Erythematous • Pseudomembranous	
Candida-associated lesions • Denture stomatitis • Angular cheilitis • Median rhomboid glossitis	
Keratinized primary lesions superinfected with Candida • Leukoplakia • Lichen planus • Lupus erythematosus	

Clinical features

It may range from mild superficial mucosal involvement to severe fatal disseminated form as seen in immunocompromised individuals.

Acute pseudomembranous oral candidiasis

- It is a common form of disease.
- It is also known as thrush.

- *Age:* Any age.
- *Site:* Buccal mucosa, tongue, palate, gingiva and floor of the mouth.
- It may be initiated by exposure of patient to broad-spectrum antibiotics or by impairment of patient's immune system.
- Soft, white, slightly raised plaques that closely resemble to milk curds.
- Plaques or pseudomembranous candidiasis may be stripped off from the mucosa, leaving a raw erythematous and bleeding surface.
- Symptoms are usually mild consisting of a burning sensation of the oral mucosa or an unpleasant taste in the mouth.
- In severe cases, the entire oral cavity and oesophagus are involved. It is common in HIV patients.
- Pseudomembrane consists of desquamated epithelium, keratin, fibrin, necrotic material, leukocyte, fungal hyphae and bacteria.

Erythematous candidiasis

(Synonyms: Antibiotic sore mouth; acute atrophic oral candidiasis)

- It includes antibiotic sore mouth, central papillary atrophy of tongue and cheilocandidiasis under this category of erythematous candidiasis.
- It occurs as sequelae to a course of broad-spectrum antibiotics, corticosteroids or any immunosuppressive diseases.
- *Site:* Any area in oral cavity.
- The lesion appear erythematous rather than white due to increased vascularity.
- It is the only variety of oral candidiasis which is painful.
- It is distinguished from erythroplakia by its diffuse border in contrast to erythroplakia, where the borders are sharp and well demarked.
- Central papillary atrophy of tongue is an asymptomatic symmetric erythematous lesion on dorsal aspect in posterior region. The erythematous appearance occurs due to the loss of filiform papillae.
- Some patients with central papillary atrophy may also exhibit signs of oral mucosal candidal infection at other sites. This presentation of erythematous candidiasis has been termed as *chronic multifocal candidiasis.*
- The palatal lesion contacts with dorsal tongue lesion when tongue is at rest—*kissing lesion,* because of the intimate proximity of involved areas.

Chronic hyperplastic oral candidiasis

(Synonym: Candidal leukoplakia)

- *Site:* Lip commissures, buccal mucosa, tongue and palate.

- It is characterized by white plaques which cannot be removed by scraping.
- It is a least common form of candidiasis.
- Plaque areas are bilateral, slightly elevated, indurated with irregular thickness.
- More common in patients infected with HIV, smoking and denture wearer.

Chronic atrophic oral candidiasis

(Synonym: Denture sore mouth)

- *Age:* Elders.
- *Sex:* Female predilection.
- *Site:* Maxillary arch.
- It is characterized by a diffuse erythematous of the denture bearing area.
- The lesion is red, oedematous and asymptomatic.
- It occurs with angular cheilitis and poor oral hygiene.

Secondary oral candidiasis

1. *Chronic localized mucocutaneous oral candidiasis*
 - *Site:* Oral mucosa, skin, nail and vagina.
 - It occurs early in life, but there is no genetic transmission.
 - It is a severe form of the disease.
 - It is a long-standing and persistent candidal infection.
 - Oral lesions are usually thick, white plaques that typically do not rub off, although the other clinical forms of candidiasis may also be seen.
2. *Chronic diffuse mucocutaneous oral candidiasis*
 - It is a least common form of candidiasis.
 - *Sex:* No sex predilection.
 - *Age:* >50 years.
 - *Site:* Limbs, face, scalp and shoulder, nail and oral cavity.
 - No familial history.
 - The lesion is extensive, raised crusty sheet and late in onset.
 - It is similar to chronic hyperplastic candidiasis.
3. *Chronic familial mucocutaneous oral candidiasis*
 - It is transmitted through genetically as autosomal recessive trait.
 - The patient exhibits varying abnormalities in his/her immune system—impaired cell-mediated immunity and isolated IgA deficiency.
 - *Age:* Before the age of 5 years.
 - *Sex:* No sex predilection.
 - A triad of mucocutaneous candidiasis, thymoma and myositis is seen.

4. *Candidiasis endocrinopathy syndrome*
(Synonym: Autoimmune polyendocrinopathy candidiasis ectodermal dystropy [APECED] syndrome)

- It is transmitted through genetically as autosomal recessive trait.
- *Age:* Adult.
- *Site:* Skin, scalp, nail and oral mucous membrane.
- It is associated with hypoparathyroidism, hypothyroidism, diabetes mellitus and Addison's disease.
- Oral findings commonly include enamel hypoplasia.

Histopathology

- The candidal organism can be seen microscopically in either an exfoliative cytologic preparation or tissue sections.
- On staining with periodic acid-Schiff (PAS) method, it can be readily identified. The PAS method stains carbohydrate, contained in abundance by fungal cell walls; the organisms are easily identified by bright magenta colour imparted by stain. To make a diagnosis of candidiasis, one must be able to see hyphae or pseudohyphae. These hyphae are approximately 2 μm in diameter, varying in their length and may show branching.
- A 10–20% potassium hydroxide (KOH) preparation may also be used to evaluate specimens for the presence of fungal organisms. With this technique, the KOH lyses the background of epithelial cells, allowing the more resistant yeasts and hyphae to visualize.
- In addition, the organisms may be cultured in a variety of media including blood agar, cornmeal agar and Sabouraud's broth.
- The common features found in tissue with candidiasis are increased thickness of parakeratin on the surface of the lesion in conjunction with elongation of epithelial rete ridges.
- Chronic inflammatory cell infiltrate can be seen in connective tissue immediately subjacent to infected epithelium.
- Small collection of neutrophils (microabscess) is often identified in parakeratin layer and the superficial spinous cell layer near the organisms.
- The candidal hyphae are embedded in parakeratin layer and rarely penetrate into the viable cell layers of epithelium unless the patient is immunocompromised.

Differential diagnosis

- Chemical burns
- Gangrenous stomatitis
- Superficial bacterial infections
- Traumatic ulcers

Prognosis and predictive factors

- To identify and eliminate predisposing or precipitating factor.
- Treat the underlying systemic conditions (diabetes, malnutrition and anaemia).
- The discontinuation of broad-spectrum antibiotics.
- Improved by good oral hygiene.
- Discontinuity of dentures, if possible.
- Administration of antifungal drugs like nystatin, amphotericin B, miconazole, clotrimazole and ketoconazole.
- ***Complications***
 - Extensive tracheal and oesophageal involvement in thrush may lead to dysphagia and respiratory distress
 - Bronchopulmonary candidiasis
 - Candidal oesophagitis
 - Endocarditis
 - Endophthalmitis
 - Meningitis

North american blastomycosis

(Synonym: Gilchrist's disease)

- In *1894, Gilchrist* first described blastomycosis in the United States.
- Blastomycosis is a granulomatous fungal infection caused by *Blastomyces dermatitidis.*
- Blastomycosis is a common infection among animals like dogs, horses, cows, cats, bats and lions. It may affect the humans also because of the shared environment.

Pathogenesis

- It occurs by inhalation of aerosolized conidial forms of the fungus from its natural soil habitat and enters the human lungs and tissue.
- Yeast forms multiply and may disseminate through the blood and lymphatics to other organs.

- There is evoked inflammatory response of neutrophils, followed by macrophage and leads to granuloma formation.

Clinical features

- **Age.** 30–70 years.
- **Sex.** Male predilection.
- **Location.** Pulmonary involvement is present in almost all cases and extra pulmonary site like skin, bone, brain, genital organ, eye, trachea, ear, larynx and breast.
- **Signs and symptoms**
 - *Acute blastomycosis:* It resembles pneumonia, characterized by high fever, chest pain, malaise, night sweats and productive cough with mucopurulent sputum. Rarely, infection may precipitate life-threatening adult respiratory distress syndrome. Skin lesions are rarely seen.
 - *Chronic blastomycosis*
 - It is more common than acute form.
 - It resembles *tuberculosis.*
 - Low-grade fever, night sweats, weight loss and productive cough.
 - Chest radiographs appear normal or may demonstrate diffuse infiltrates or one/more pulmonary or hilar masses. Calcifications are not seen.
 - Cutaneous lesion represents the spread of infection from lungs.
 - *Skin lesions*
 - These are more common on the face, neck and extremities.
 - Initially, the lesions are sharply demarcated papules which gradually form tiny miliary abscesses or pustules. Later, they discharge the pus and form ulcerated lesions. Few lesions show verrucous, with raised irregular borders.
 - These may show central healing and scar formation.
- ***Oral manifestations***
 - It resembles manifestations of *actinomycosis.*
 - Abscess formation results in ulcer and draining sinus.
 - These lesions may have an irregular, erythematous or white intact surface or they may appear as ulcerations with irregular rolled borders and varying degree of pain.
 - Loosening of teeth.
 - Oropharyngeal pain and cervical lymphadenopathy.

Histopathology

- It shows a mixture of acute inflammation and granulomatous inflammation surrounding variable numbers of yeasts.
- These organisms are 8–20 μm in diameter. These are characterized by doubly refractile cell wall and a broad attachment between the budding cell and parent cell. These organisms can be detected by PAS stain and Grocott–Gomori methenamine silver stain.
- Epithelium shows pseudoepitheliomatous hyperplasia, sometimes ulcerated.
- Sometimes, microabscess formation is seen.

Prognosis and predictive factors

Administration of amphotericin B is advised.

South american blastomycosis

(Synonyms: Paracoccidioidomycosis; Lutz's disease)

It is a serious, systemic mycotic infection caused by the fungus *Paracoccidioides brasiliensis*.

Pathogenesis

- The disease is caused by the inhalation of the fungus *P. brasiliensis.*
- *P. brasiliensis* is a thermally dimorphic fungus that grows as a mycelium in soil; its natural habitat is not well understood.
- Initially, disease is acquired through the inhalation and transforms into yeast cells within the alveolar macrophages and causes granuloma in multiple tissues like lung, mucous membranes, skin, lymph nodes and various internal organs.
- The incubation period is few weeks to decades.
- South American blastomycosis has been identified as an AIDS-associated opportunistic infection.

Clinical features

- **Age.** 30–50 years.
- **Sex.** Male predilection: This may be due to protective effect of female hormones, because β-estradiol inhibits the transformation of hyphal form of organism to pathogenic yeast form.

- **Location.** Lungs, larynx, pharynx, GIT, CNS and skin.
- **Signs and symptoms**
 - It appears initially as pulmonary infections after exposure of spores of the organisms.
 - Infection is generally self-limiting. It may spread by a haematogenous or lymphatic route to a variety of tissues including lymph nodes, skin and adrenal glands.
 - Low-grade fever, malaise and weight loss are commonly seen.
 - Laryngeal and pharyngeal lesions can cause dysphagia, hoarseness or strider.
 - *Respiratory system:* Cough; mucous production, which may be blood-tinged; and dyspnoea.
 - *GIT:* Abdominal pain.
 - *CNS:* Headache, meningitis.
 - Adrenal involvement often results in hypoadrenocorticism (Addison's disease).
 - *Skin:* It occurs most commonly on the face. It may be papular, nodular, ulcerated, papillomatous, or even tuberous. Occasionally, haematogenous spread results in widely scattered lesions and subcutaneous abscesses.
 - *Lymph nodes:* Extensive lymphadenopathy develops. Cervical lymph nodes are commonly affected. Nodes are hypertrophic, firm and painful.
 - Hepatosplenomegaly.
 - Intestinal ulcerations and osteomyelitis are also seen.
 - *Oral manifestations*
 - Site: Lips, gingiva, palate, buccal mucosa and tongue.
 - Organisms enter through the periodontal membrane and reach the regional lymph nodes.
 - Lesions begin as papules or plaques, which slowly enlarge and coalesce to form ulcer.
 - The lesions typically have granulomatous, mulberry-like surfaces.
 - Lesions progress over months and are painful.
 - Loss of teeth may occur.

Histopathology

- Pseudoepitheliomatous hyperplasia with intraepidermal abscesses and sometimes, ulceration of overlying surface epithelium are seen.

- It reveals a granulomatous reaction with epithelioid cells, multinucleated giant cells and severe inflammatory infiltrate around the caseous necrosis.
- Spores may be found within giant cells or free in the inflammatory infiltrate.
- Scattered, large (up to 60 μm in diameter) yeasts are readily identified after staining of tissue sections with Grocott–Gomori methenamine silver stain or PAS method.
- The organisms often show multiple daughter buds on parent cell, resulting in appearance as resembling *'Mickey Mouse ears'* or *'the spokes of a ship's steering wheel (Mariner's wheel)'*.

Note
Fungus of South American form: 10–60 μm
Fungus of North American form: 5–15 μm

Coccidioidomycosis

(Synonyms: San Joaquin Valley fever; Valley fever)
Coccidioides immitis, a soil fungus, is the responsible agent for coccidioidomycosis.

Pathogenesis

- *C. immitis* infection occurs when inhaled anthroconidia (anthrospores) are deposited in the lower airways and subsequently change its morphology into nonbudding spherules, measuring 10–80 μm in diameter.
- These spherules enlarge, divide and rupture, releasing hundreds of 2–5 μm spherule particles (endospores) which are similarly developed into full size spherules and reproduce.

Clinical features

- **Age.** Any age group.
- **Sex.** No sex predilection.
- **Location.** Lungs, pharynx, larynx and skin.
- **Signs and symptoms:** There are two basic forms of the disease:
 1. Primary nondisseminated coccidioidomycosis
 2. Progressive disseminated coccidioidomycosis

Primary nondisseminated coccidioidomycosis

- Common symptoms are fever, cough, chest pain, fatigue, dyspnoea, headache, arthralgias and myalgias.
- *Erythema nodosum:* A condition that usually affects the skin of legs and is characterized by the appearance of multiple tender, erythematous nodules in the subcutaneous connective tissue.
- Sometimes, skin lesions can also present as ulcerations or verrucous lesions at the nasolabial area.
- Pulmonary cavitation or fibrosis or calcified nodules may occur.
- Occasionally, immune response may trigger a hypersensitivity reaction that causes development of an *erythema multiforme.*
- This form of the disease is self-limiting and runs its course within 10–14 days.

Progressive disseminated coccidioidomycosis

- It occurs rarely, but it is a more serious condition.
- The disease course is rapid and extend from the lungs to various viscera, bones, joints, skin, CNS, cardiovascular system and musculoskeletal system.
- CNS involvement causes meningitis, which is the most frequent cause of death.
- *Cutaneous lesions*
 - It appears as papules, subcutaneous abscesses, verrucous plaques, granulomatous nodules and ulcerated lesions.
 - *Site:* Area of central face like nasolabial fold.
 - These lesions tend to heal by hyalinization and scar.
- Dissemination to bone results in osteomyelitis.
- Immunosuppression increases the risk of dissemination.

The following groups are more susceptible for this infection:

- Patients taking large doses of systemic corticosteroids (organ transplant recipients)
- Patients who are being treated with cancer chemotherapy
- Patients in the end stages of HIV infection
- Patients who are pregnant
- *Oral manifestations*
 - Lesions are proliferative granulomatous and ulcerated.
 - Lesions tend to heal by hyalinization and scar.
 - Lytic lesions of the jaw.

Histopathology

- It shows *granuloma,* which consists of central coagulation necrosis, surrounded by large mononuclear cells, lymphocytes, plasma cells and few giant cells scattered throughout the lesion, but epithelioid cells are not seen.
- The organisms are often present in cytoplasm of the giant cells.
- In tissue sections, the organisms will be found in various sizes and generally show no budding.
- The endospores within the large spherules can be identified without difficulty. Although special stains like PAS, Grocott–Gomori methenamine silver staining methods enable pathologists to identify organisms.

Prognosis and predictive factors

It should be treated with amphotericin B, ketoconazole, fluconazole or itraconazole.

Histoplasmosis

(Synonym: Darling's disease)

- Histoplasmosis is the most common endemic fungal infection, caused by *Histoplasma* capsulatum.
- It is acquired by inhalation of dust containing the spores of the fungus.
- Excretion of birds like pigeons, bats and black birds contaminate the soil, thereby enriching the growth medium for the fungus. Birds cannot be infected by the fungus and do not transmit the disease.

Pathogenesis

- *H. capsulatum* is in the mycelial form, later it is converted to the yeast form under temperature-controlled regulation.
- Air-borne spores of organisms are inhaled, pass into the terminal passages of lungs and germinate.
- T lymphocytes are crucial in limiting the extent of infection and phagocytosis by macrophages in which the yeast gets replicated in approximately 15–18 hours.
- As the host immunity response develops, yeast growth stops within 1–2 weeks after exposure.
- Over weeks to months, the inflammatory response produces calcified fibrinous granulomas with areas of caseous necrosis.

Clinical features

- **Age.** Any age group.
- **Sex.** No sex predilection.
- **Location.** Lungs, oesophagus and visceral organs.
- **Signs and symptoms**
 - It produces either no symptoms or mild symptoms for which the patient does not seek medical treatment.
 - The expression of disease depends on the quantity of spores inhaled, the immune status of the host and strain of *H. capsulatum.* Individuals may remain normal, if they inhale little number of spores. Therefore, they have either no symptoms or have a mild flu-like illness for 1–2 weeks.
 - *Acute histoplasmosis*
 - It is a self-limiting pulmonary infection that probably develops in individuals exposed to low number of spores.
 - With high concentration of spores, individuals may experience acute symptoms.
 - Fever, headache, malaise, weight loss, myalgia, abdominal pain and chills are present.
 - Calcification of hilar lymph nodes may be detected years later in chest radiographs.
 - *Chronic histoplasmosis*
 - Primarily, it affects the lungs, although it is much less common than acute form.
 - Usually, it affects older, emphysematous or immunosuppressive patients.
 - Clinically, it appears similar to tuberculosis—cough, weight loss, fever, dyspnoea, chest pain, haemoptysis, weakness and fatigue.
 - Chest radiographs show upper lobe infiltration and cavitation.
 - *Oral manifestations*
 - *Site:* Buccal mucosa, gingival, tongue, palate and lips.
 - The lesion appears as a solitary, painful ulceration of several weeks duration. Ulcerated area is usually covered by nonspecific grey membrane and is indurated. The ulcerated lesions have firm, rolled margins resembling malignancy.
 - Some lesions may appear erythematous or white with an irregular surface.

Histopathology

- It shows either a diffuse infiltrate of macrophages or more commonly as granuloma. It is characterized by the areas of caseation necrosis surrounded by circulating neutrophils, monocytes, macrophages and few multinucleated giant cells.
- The organisms can be identified with some difficulty in routine H and E stained section; however, special stains such as PAS and Grocott–Gomori methenamine silver stain methods.
- The organisms are found in the phagocytic cells and appear as tiny intracellular structures measuring little more than 1 μm diameter.
- The organisms may be readily isolated by inoculating the tissue on to blood agar containing penicillin and streptomycin.

Prognosis and predictive factors

- Pulmonary type will resolve spontaneously.
- Sometimes, surgical procedures are used.
- Administration of amphotericin B is advised.

Cryptococcus

(Synonyms: European blastomycosis; torulosis)

- It is a chronic fungal infection caused by *Cryptococcus neoformans* and *Cryptococcus bacillispora*.
- The organisms can harbour from the pigeon.
- It occurs by the inhalation of air-borne microorganisms.
- It is an opportunistic infection; hence it is more prone to occur in the immunosuppressive patients.

Pathogenesis

This disease is acquired by inhalation of *C. neoformans* spore into the lungs, resulting in an immediate influx of neutrophils, which destroys most of the yeasts. Macrophages soon follow, although resolution of infection in the immunocompetent host ultimately depends on an intact cell-mediated immune system.

Clinical features

- **Age.** Middle age group.
- **Sex.** Male predilection.
- **Location.** Skin, oral mucosa, subcutaneous tissue, lungs, joints and

meninges.

- **Signs and symptoms**
 - *Skin lesions:* Multiple brown papule which leads to ulceration and discharging a pus-like material rich in cryptococcal organisms.
 - *Lung:* Cough, chest pain, fever, malaise and pneumonitis.
 - *CNS:* Various neurological signs and increased intracranial pressure. Cryptococcal meningitis may occur.
 - Cryptococcosis has been reported in patients suffering from malignant lymphoma, evidence of opportunistic nature of disease.
 - *Oral manifestations*
 - Rare.
 - They manifest either as crater-like, nonhealing single or multiple ulcers that are tender on palpation or as friable papillary erythematous plaques.
 - Dissemination to salivary gland tissue is rarely reported.

Histopathology

- Granuloma is characterized by the epithelioid cells, multinucleated giant cells, inflammatory cells and there is absence of focal necrosis.
- Organism may be single or multiple in granuloma.
- Causative organism is a gram-positive, budding, yeast-like cell with an extremely thick, gelatinous capsule.
- Cryptococcus measures 5–20 μm in diameter and in tissue sections, it appears as a small organism with a large clear halo, sometimes described as tissue microcysts.
- Organisms can be demonstrated using special stains like PAS, mucicarmine, Grocott–Gomori methenamine silver stain methods.

Prognosis and predictive factors

- Administration of amphotericin B.
- Prognosis is variable depending upon the site of involvement.

Zygomycosis

(Synonyms: Mucormycosis; phycomycosis)

- Zygomycosis is an opportunistic, frequently fulminant fungal infection that is caused by the class zygomycetes including genera such as *Absidia, Mucor, Rhizomucor* and *Rhizopus.*
- It is the third most common cause of invasive fungal infection in

immunocompromised patients, especially in stem cell transplant recipients and patients with underlying hematologic malignancies, malignant lymphoma and diabetic patients.

Pathogenesis

- The pathogens that cause zygomycosis are commonly found in the environment on fruit, on bread and in soil, and are common components of decaying organic debris.
- They enter tissue through nasal mucosa and extend to the paranasal sinuses, pharynx, palate, orbit and brain.
- Zygomycosis is noted in insulin-dependent diabetes individuals who have uncontrolled diabetes and ketoacidosis.
- Ketoacidosis inhibits the binding of iron to transferrin, allowing serum iron levels to rise.
- The growth of these fungi is enhanced by iron, and patients who are taking deferoxamine (an iron chelating agent used in the treatment of diseases such as thalassaemia) are also at increased risk of developing zygomycosis.

Clinical features

- **Age.** Any age group.
- **Sex.** Male predilection.
- **Signs and symptoms**
 - Two types of phycomycosis occurs in human beings:
 - *Superficial form* involves the external ear, fingernail and skin.
 - *Visceral form* includes the pulmonary, gastrointestinal and rhinocerebral.
 - Zygomycosis may involve any area of the body, but the rhinocerebral form is most relevant to oral health care provider.
 - Symptoms of lung (pulmonary) mucormycosis include cough and shortness of breath.
 - Symptoms of gastrointestinal mucormycosis are abdominal pain and vomiting blood.
 - Symptom of cutaneous zygomycosis: Single skin lesions that begin with induration and erythema and gradually develop into a necrotic ulcer with a characteristic dark central area. The margins of the ulcer are sharply demarcated.
 - Symptoms of rhinocerebral mucormycosis include:

- Eye swelling and protrusion (proptosis)
- Dark reddish black nasal turbinate
- Nasal discharge
- Fever
- Headache
- Sinus pain or congestion
- Necrosis may extend to paranasal sinuses and orbital cavity
- Development of sinus tract and sloughing of tissue is common
- Maxillary sinus involvement
- *Oral manifestations*
 - It presents as intraoral swelling of maxillary alveolar process, the palate or both.
 - If condition remains untreated, palatal ulceration may evolve with surface of ulcers typically appears black and necrotic.
 - Massive tissue destruction may occur, if the condition is not treated.
- *Radiological features:* Opacification of lesion tissue in sinuses may be observed in conjunction with patchy effacement of the bony walls of the sinuses.

Histopathology

- Lesional tissue shows extensive amount of necrosis with numerous large (6–30 μm), branching, nonseptate hyphae at the periphery. The hyphae tend to branch at 90° angle.
- The disease is attributable to the fungus predilection for blood vessels. It is able to penetrate the blood vessel wall and produce thromboses.
- A neutrophilic infiltrate usually predominates in viable tissue but host inflammatory cell response to the infection may be minimal, particularly if the patient is immunosuppressed.

Prognosis and predictive factors

Institute early and appropriate antifungal administration.

- Remove as much devitalized tissue by wide surgical debridement.
- ***Complications***
 - Blindness (if the optic nerve is involved)
 - Clotting or blockage of brain or lung blood vessels (thrombosis)
 - Death
 - Nerve damage

Deep fungal infections are described in Table 6.2.

Table 6.2

Deep fungal infections

Infection	Organisms	Size (μm)	Characteristics	Morphology
Histoplasmosis	*Histoplasma capsulatum*	2–5	Yeast in macrophages	
Coccidioidomycosis	*Coccidioides immitis*	30–60	Endospores in spherules	
Blastomycosis	*Blastomyces dermatitidis*	8–15	Budding yeasts	
Cryptococcosis	*Cryptococcus neoformans*	2–15	Yeasts with thick capsule	

Key points

Bacterial infections

- *Tuberculosis* is caused by *Mycobacterium tuberculosis.* It is a rod-shaped, aerobic, nonmotile, nonspore forming and slow-growing bacterium.
- *Scrofula:* Enlargement of lymphoid tissue due to tuberculosis infection caused by drinking contaminated milk.
- *Paucibacillary leprosy (tuberculoid leprosy):* Skin lesions with no bacilli in smear.
- *Multibacillary leprosy (lepromatous leprosy):* Skin lesions with bacilli in smear.
- *Actinomycosis* is a chronic suppurative and granulomatous inflammation, which shows multiple abscesses and sinus tracts with sulphur-like granules discharge.
- *Tetanus* is an acute infectious disease of the nervous system characterized by intense activity of motor neurons and resulting in severe muscle spasms.
- *Syphilis* is caused by a spirochaete *Treponema pallidum.*
- *Primary syphilis:* Chancre—3 weeks after initial exposure.
- *Secondary syphilis:* Mucous patch—3 months after initial exposure.
- *Tertiary syphilis:* Gumma—3 years after initial exposure.
- Gonorrhoea is a common sexually transmitted infection caused by

https://t.me/RoyalDentistryLibrary/

Neisseria gonorrhoeae.

Viral infections

- *HSV-1,* affects above the waist (orofacial disease).
- *HSV-2,* affects below the waist (genital disease).
- *Lipschutz bodies,* eosinophilic intranuclear inclusion bodies seen in HSV-infected epithelial cells.
- *Ramsay Hunt syndrome*, caused by VZV reactivation involving facial and auditory nerves.
- *Koplik's spots* are bluish white macules or greyish spots on buccal and labial mucosa.
- *Forchheimer's sign:* Rubeola, roseola, infectious mononucleosis and scarlet fever.
- *Henderson–Patterson inclusion bodies,* basophilic intracytoplasmic inclusions seen in molluscum contagiosum infected epithelial cells.
- *AIDS* is caused by human immunodeficiency virus (HIV), which destroys the immune system by affecting CD4 T lymphocyte and leads to numerous opportunistic infections, neoplasms and neurological disorders.
- HIV can spread through sexual contact, blood transfusions, accidental needle sticks, needle sharing or from mother to child.

Fungal infections

- *Candida albicans* is a common inhabitant of the oral cavity, vagina, gastrointestinal tract of normal person. It causes thrush when normal host immunity or normal host flora is disrupted.
- *Erythematous candidiasis* occurs as a sequelae to a course of broad-spectrum antibiotics, corticosteroids or any immunosuppressive diseases.
- *Secondary candidiasis* occurs as a result of disease such as a thymic aplasia and candidiasis endocrinopathy syndrome.
- *Paracoccidioides brasiliensis (paracoccidioidomycosis)* microorganisms show multiple daughter buds on parent cell resulting in 'Mickey Mouse ears' appearance.
- *Zygomycosis* commonly occurs among insulin-dependent diabetes individuals.
- *Aspergillosis* causes mass of fungal hyphae in maxillary sinus —*aspergilloma,* which may undergo dystrophic calcification in sinus —*antrolith.*

https://t.me/RoyalDentistryLibrary/

- Deep fungal infections.
 - *Histoplasmosis: Histoplasma capsulatum*—2–5 μm.
 - *Coccidiodomycosis: Coccidioides immitis*—30–60 μm.
 - *Blastomycosis: Blastomyces dermatitidis*—8–15 μm.
 - *Cryptococcosis:* Cryptococcus neoformans—2–15 μm.

Frequently asked questions

Bacterial infections

1. Scarlet fever.
2. Discuss pathogenesis, clinical features, histopathology and diagnosis of tuberculosis.
3. Tuberculoid leprosy.
4. Lepromatous leprosy.
5. Actinomycosis/histopathology of actinomycosis.
6. Discuss pathogenesis, clinical features, histopathology and diagnosis of syphilis.
7. Congenital syphilis/chancre/primary syphilis/secondary syphilis/tertiary syphilis.
8. Noma.
9. Discuss pathogenesis, clinical features and histopathology pyogenic granuloma.

Viral infections

1. Classify viral infections and discuss pathogenesis, clinical features and histopathology of herpes simplex infection.
2. Herpes zoster infections/chickenpox/varicella/shingles/Ramsay Hunt syndrome.
3. Rubeola.
4. Molluscum contagiosum.
5. Mumps.
6. Write pathogenesis, clinical features, histopathology and diagnosis of HIV.
7. AIDS.
8. Oral manifestations of HIV.

Fungal infections

1. Discuss pathogenesis, clinical features, histopathology and diagnosis of

https://t.me/RoyalDentistryLibrary/

oral candidiasis.

2. North American blastomycosis.
3. Paracoccidioidomycosis.
4. Coccidioidomycosis.
5. Hystoplasmosis.
6. Write about pathogenesis, clinical features, histopathology of mucormycosis.

https://t.me/RoyalDentistryLibrary/

CHAPTER 7

https://t.me/RoyalDentistryLibrary/

Diseases of the periodontium

https://t.me/RoyalDentistryLibrary/

Healthy periodontium

Periodontium is the attachment apparatus of the teeth and consists of cementum, periodontal ligament, alveolar bone and a portion of the gingiva.

Gingiva

The gingiva is defined as the part of the oral mucosa that covers the alveolar processes of the jaws and surrounds the necks of the teeth.

- Gingiva is divided anatomically into marginal, attached and interdental gingiva.
- The marginal or unattached gingiva is the terminal edge or border of the gingiva surrounding the teeth in collar-like fashion. It can be demarcated from the adjacent attached gingiva by a shallow linear depression—*the free gingival groove.*
- Interdentally, the gingiva adapts its shape to the form, size and position of adjacent teeth. Interdental portion of the gingiva is narrow between the front teeth and broader between the premolars and molars.
- The attached gingiva extends from the mucogingival junction to the projection on the external surface of the bottom of the gingival sulcus or pocket. The width of the attached gingiva on the facial aspect differs in different areas of the mouth. It is generally greatest in the incisor region (3.5 to 4.5 mm) and less in the posterior segments with the least width in the first premolar area (1.9 mm).
- **Functions**
 - It connects soft tissue to hard tissue which establishes a seal around the tooth.
 - It controls oral microbes from invasion.
 - It protects the periodontal ligament and alveolar bone from insulations.
 - It adapts to changing oral conditions and eruption.

Periodontal ligament

- It is composed of collagen fibres arranged in bundles that are attached from the cementum of the tooth to the alveolar bone.
- In humans, the width of the periodontal ligament ranges from 0.15 to 0.38 mm.
- The principal fibres of periodontal ligament are as follows:
 - *Alveolar crest fibres:* These fibres radiates from the crest of the alveolar process and attaches to the cervical part of the cementum.

https://t.me/RoyalDentistryLibrary/

- *Horizontal fibres:* These fibres run at right angles to the long axis of the tooth from cementum to the alveolar bone.
- *Oblique fibres:* These fibres extend from the cementum in the coronal direction obliquely to the bone.
- *Apical fibres:* These fibres run from the cementum to the bone in an irregular manner at the apical portion of the tooth socket.
- *Interradicular fibres:* These fibres extend from the interradicular cementum of multirooted teeth to the crest of the interradicular bone.

- **Functions**
 - Physical
 - Resistance to impact occlusal forces
 - Transmits occlusal forces on to bone
 - Formative and remodelling function
 - Nutritional and sensory function

Cementum

- Cementum is a mineralized tissue covering the root surfaces of the tooth.
- It anchors the principal collagen fibres of the periodontal ligament to the root surface of tooth.
- It has important adaptive and reparative functions.
- Cementum maintains occlusal relationship, integrity of the root surface and tooth support.

Alveolar bone

- Alveolar process is the part of the maxilla and the mandible containing the sockets, which protects and supports the tooth.
- The main function is to distribute and resorb forces generated by mastication.
- Isolated areas in which the root is denuded of bone and the root surface is covered by periosteum and overlying gingiva are termed as *fenestrations*. In fenestrations, the marginal bone is intact. When such denuded areas extend through the marginal bone, the defect is termed as *dehiscence.*

Classification of periodontal diseases

Periodontal diseases are classified as follows:

- **Gingivitis**
 - Plaque-induced gingivitis

https://t.me/RoyalDentistryLibrary/

- Non-plaque-induced gingivitis
- **Chronic periodontitis**
 - Localized
 - Generalized
- **Aggressive periodontitis**
 - Localized
 - Generalized

Periodontitis as a manifestation of systemic disease

- **Necrotizing periodontal disease**
 - Necrotizing ulcerative gingivitis (NUG)
 - Necrotizing ulcerative periodontitis (NUP)
- **Abscesses of periodontium**
 - Gingival abscess
 - Periodontal abscess
 - Pericoronal abscess
- **Periodontitis associated with endodontic lesions**
 - Endodontic-periodontal lesion
 - Periodontal-endodontic lesion
 - Combined lesion
- **Developmental or acquired deformities and conditions**
 - Localized tooth-related factors that predispose to plaque-induced gingival diseases or periodontitis
 - Mucogingival deformities and conditions around teeth
 - Mucogingival deformities and conditions on edentulous ridges
- **Occlusal trauma**

https://t.me/RoyalDentistryLibrary/

Gingival diseases

Gingivitis

Inflammation of the gingiva is known as *gingivitis*.

- Gingivitis can be classified into:
 - Plaque-induced gingivitis
 - Non-plaque-induced gingivitis
- Gingivitis is also classified on the basis of duration and onset of disease as follows:
 - *Acute gingivitis:* It is sudden in onset, shorter duration and can be painful.
 - *Recurrent gingivitis:* Gingivitis disappears spontaneously after the treatment.
 - *Chronic gingivitis:* It is of slow onset and longer duration, which is usually painless, but becomes painful in acute or subacute exacerbation.
- Gingivitis can be classified on the basis of distribution as follows:
 - *Localized gingivitis:* It is confined to the gingiva of a single tooth.
 - *Generalized gingivitis:* It involves gingiva of all the teeth in the oral cavity.
 - *Marginal gingivitis:* Gingivitis involves the gingival margin and a portion of attached gingiva.
 - *Papillary gingivitis:* Gingivitis involves interdental papilla.

Clinical features

- The earliest symptoms of gingivitis are loss of stippling and bleeding from the gingival sulcus on gentle probing.
- Gingiva becomes red due to increase in vascularization. The colour change starts in the interdental papillae, gingival margins and spread to the attached gingiva.
- The consistency of gingival may be spongy.

1. Plaque-induced gingivitis

- It is most common form of gingival disease.
- It occurs on a periodontium with no attachment loss or on a periodontium with a previous attachment loss that is stable and not progressing.

Pathogenesis

https://t.me/RoyalDentistryLibrary/

- Due to poor oral hygiene, there is increase in normal microflora such as *Streptococcus*, *Actinomyces*, etc. which produce toxins that cause an inflammatory reaction.
- Plaque-induced gingival disease is the result of the interaction of plaque, bacteria and defence cells of the host.
- This bacteria and host interaction is modified by local and systemic factors. The factors that have been most commonly cited are given below.

a. local factors

- Microorganisms
- Calculus
- Food impaction
- Faulty or irritating restorations or appliances
- Mouth breathing
- Tooth malposition

b. systemic factors

- Nutritional deficiencies
- Drug action
- Endocrine changes associated with puberty, pregnancy, menstrual cycle and diabetes mellitus
- Allergy
- Specific granulomatous infections
- Neutrophil dysfunction
- Immunopathies

Microorganisms

- *Actinomyces* is the dominant genus in the supragingival plaque.
- Various types of bacilli, cocci, fusiform organisms, spirochaetes, and in advanced periodontitis amoebas and trichomonads are seen.
- There are many destructive enzymes released by polymorphoneutrophils (PMNs) and numerous tissue-destructive lymphokines and lymphotoxins elaborated by B or T lymphocytes. Thus, collagenase liberated by both PMNs and lymphocytes, other lysosomal enzyme secretions, lysosomal acid hydrolases of macrophages, lymphotoxin-mediated cytokines and osteoclast-activating factor (OAF) are all tissue-destructive substances released as part of the inflammatory reaction to injury.
 Calculus: Calculus causes irritation for the gingival tissue. This irritation

https://t.me/RoyalDentistryLibrary/

is probably caused by the by-products of the microorganisms, although the mechanical friction resulting from the hard, rough surface of the calculus.

Food impaction: The impaction of food and the accumulation of debris on the teeth because of oral hygiene neglect result in gingivitis.

Faulty and irritating restorations or appliances: Faulty restorations may act as irritants to gingival tissues and thereby induce gingivitis. Overhanging margins of proximal restorations may directly irritate the gingiva and in addition allow the collection of food debris and organisms that further injure these tissues. Prosthetic or orthodontic appliances impinging on the gingival tissues produce gingivitis as a result of pressure and trapping of food and microorganisms.

Mouth breathing: Drying of the oral mucous membrane due to mouth breathing habit, excessive environmental heat or excessive smoking causes gingival irritation, with accompanying inflammation or sometimes hyperplasia.

Tooth malposition: Teeth which are erupted or which have been moved out of physiologic occlusion, where they are repeatedly subjected to abnormal forces during mastication, are apparently very susceptible to the development of periodontal disease.

Diabetes mellitus: The relationship between diabetes and gingival disease is unclear. Although it is commonly held that periodontal disease is more severe and progresses faster in both type I and II diabetics than in nondiabetics, the evidence is inconclusive. Vascular changes and defects in cellular defence mechanisms have been suggested as possible ways in which diabetes could increase susceptibility to gingival disease.

Drugs: Many drugs are potentially capable of inducing gingivitis, particularly an acute gingivitis, owing to a direct local or systemic irritating action. Phenol, silver nitrate, volatile oils or aspirin, if applied on the gingiva, will provoke an inflammatory reaction. Dilantin sodium, cyclosporine or calcium channel blockers induce gingival enlargement.

Pregnancy and sex hormones: Several studies have shown that the severity of a pre-existing gingivitis increases in pregnancy from 2nd to 8th month of gestation and then decreases. Hormonal changes modify the tissue response to dental plaque and increased levels of sex hormones or their metabolites are found in inflamed gingiva. Experimental evidence suggests that the aggravation of gingivitis

during pregnancy is related mainly to progesterone which affects the function and permeability of the gingival microvasculature. Localized gingival hyperplasia also occurs during pregnancy (pregnancy epulis). Increased levels of gingivitis occurring around puberty and in some women taking oral contraceptives may also be related to the concentration of circulating sex hormones.

Nutritional disturbances: Severe and prolonged deficiency of vitamin C causes scurvy which may be associated with haemorrhagic gingivitis and oedematous enlargement of the gums, but these are not constant features. The effects of nutritional deficiencies on periodontium is explained in Chapter 14 Oral Aspects of Metabolic Disorders.

Clinical features

Acute gingivitis: It is a painful uncommon lesion with sudden onset and shorter duration. In gingivitis, the inflammation is limited only to the gingiva without underlying attachment loss. It may be localized or generalized. Gingivitis involving only marginal gingiva is known as *marginal gingivitis* or *interdental papilla* or *papillary gingivitis*. When hyperaemia and swelling of the marginal gingiva are confined to a localized area of the gingiva, it assumes a crescent shape and has been termed a traumatic crescent. Diffuse gingivitis affects marginal gingiva, attached gingiva and interdental papilla.

Chronic gingivitis: It shows slight alterations in colour of the free or marginal gingiva from a light to a deeper hue of pink, progressing to red or reddish blue as the hyperaemia and inflammatory infiltrate become more intense. Bleeding may occur from the gingival sulcus following even mild irritation. Oedematous swelling of the gingiva and loss of stippling are seen. When there is marked enlargement due to oedema and fibrosis as a result of chronic inflammation, the process is called *chronic hyperplastic gingivitis.* Suppuration of the gingiva, manifested by the ability to express pus from the gingival sulcus by pressure, may occur in advanced chronic gingivitis.

Histopathology

- Gingivitis demonstrates a light inflammatory infiltrate consisting of polymorphonuclear leukocytes that accumulate in the connective tissue adjacent to sulcular epithelium. With progression, the infiltrate becomes more intense and demonstrates a mixture of lymphocytes, plasma cells

and acute inflammatory cells.

- ***Stages of gingivitis***
 - *Stage 1:* Vascular changes occur consisting essentially of dilatation of capillaries and increased blood flow. It occurs within 2–4 days of plaque accumulation.
 - *Stage 2:* It occurs in 4–7 days of plaque accumulation. Clinical signs of erythema appear mainly owing to the proliferation of capillaries and increased formation of capillary loops between rete pegs or ridges.
 - *Stage 3:* The lesion develops generally after 14–21 days of plaque accumulation. Blood vessels become engorged and congested, venous return is impaired and blood flow becomes sluggish.

Prognosis and predictive factors

- Mechanical removal of dental plaque can be aided by the use of numerous chemical agents such as chlorhexidine or triclosan.
- If there is poor response to good local therapy, a search should be made for systemic factors, which might be complicating the case.

2. Non-plaque-induced gingivitis

Non-plaque-induced gingivitis has different aetiology and characteristic clinical presentation. Non-plaque-induced gingival diseases include specific bacterial, viral and fungal infections and gingival manifestations of certain dermatoses.

- Gingival diseases of specific bacterial origin
 - *Neisseria gonorrhoeae*
 - *Treponema pallidum*
 - *Streptococcus* species
- Gingival diseases of viral origin
 - Herpes virus infection
 - Herpes zoster infection
 - Others
- Gingival diseases of fungal origin
 - Candidiasis
 - Linear gingival erythema
 - Histoplasmosis
 - Others
- Gingival lesions of genetic origin
 - Hereditary gingival fibromatosis

- Others
- Gingival manifestations of systemic conditions
 - Mucocutaneous lesions
 - Lichen planus
 - Pemphigoid
 - Pemphigus vulgaris
 - Erythema multiforme
 - Lupus erythematosus
 - Drug-induced
 - Others
 - Allergic reactions
 - Dental restorative materials
 - Reactions attributable to dentifrices, mouthwashes, chewing gum additives
 - Others
- Traumatic lesions
 - Physical injury
 - Chemical injury
 - Thermal injury
 - Foreign body reactions
 - Not otherwise specified

Necrotizing ulcerative gingivitis

(Synonyms: Vincent's infection; trench mouth; phagedenic gingivitis; fusospirochetal gingivitis)

- Necrotizing ulcerative gingivitis (NUG) is an endogenous oral infection that is characterized by necrosis of gingiva.
- It is also called as *trench mouth* due to its prevalence in combat trenches.
- Tissue destruction is caused by endogenous organisms that act either on tissue or indirectly by triggering an inflammatory reaction.
- This inflammatory condition involves primarily the free gingival margin, the crest of the gingiva and interdental papillae.
- Rarely, the lesion spreads to the soft palate and tonsillar areas and in such instances the term *Vincent's angina* has been applied.
- Pain, interdental ulceration and gingival bleeding are considered to be the diagnostic triad.
- Necrotizing ulcerative gingivitis can cause destruction of the supporting

tissues of the tooth and is termed as *necrotizing ulcerative periodontitis,* when bone loss occurs.

Pathogenesis

- It is caused by *Fusiform bacilli* and *Borrelia vincentii*—spirochaetes. In addition, *Bacteroides intermedius* and *Bacteroides melaninogenicus* may also be responsible for NUG.
- The infection frequently occurs in the presence of psychological stress. Stress-related corticosteroids are thought to alter T4/T8 lymphocytes ratio and may cause the decreased neutrophilic chemotaxis and phagocytic response seen in patients with NUG. Stress-related epinephrine may result in localized ischaemia, which predisposes to NUG.
- Other factors related to increase the frequency of NUG are, immunosuppression, smoking, local trauma, poor nutritional status, poor oral hygiene, inadequate sleep and recent illness.
- HIV-positive patients suffer from a severe form of NUG as the immune function deteriorates and progresses to HIV-associated periodontitis.

Clinical features

- **Age.** 16–30 years.
- **Gender.** No sex predilection.
- **Signs and symptoms**
 - Onset of the disease is sudden with pain, tenderness, profuse salivation and metallic taste.
 - Spontaneous bleeding from gingival tissue occurs.
 - Teeth seem slightly extruded and slightly mobile; patient is unable to eat properly.
 - The typical fetid odour ultimately develops, which is extremely unpleasant.
 - Gingiva may become stained with brown colour, there is blunting of interdental papilla.
 - A typical lesion consists of necrotic punched out, crater-like ulcerations, which is commonly developed on the interdental papilla and marginal gingiva. The surface of the gingival crater is covered by grey, pseudomembranous slough, demarcated from the reminder of the gingival mucosa by pronounced linear erythema. Removal of the lesion leaves raw surface.
 - There may be headache, malaise, low-grade fever and regional

lymphadenopathy.

- In advanced cases, there may be generalized or systemic manifestations which include leukocytosis, gastrointestinal disturbances and tachycardia.

Histopathology

- The histopathologic features of NUG are not specific.
- Typically, affected gingival papillae demonstrate surface ulceration that is covered by a thickened fibrinopurulent membrane.
- The underlying lamina propria shows an intense acute or mixed inflammatory infiltrate and extensive hyperaemia.
- Nonulcerative epithelium shows loss of typical surface keratinization.
- **Zones:** In electron microscopic investigation, four zones associated with the gingival lesion of NUG are identified:
 1. *Bacterial zone:* It is composed of a large mass of bacteria with varying morphotypes, including some spirochaetes.
 2. *Neutrophil-rich zone:* It underlies the bacterial zone, which contains many leukocytes with predominant neutrophils. Bacteria including many spirochaetes are located between the cells.
 3. *Necrotic zone:* It is characterized by disintegrating cells and many spirochaetes (large and intermediate) and other bacteria that appear to be *fusiform.*
 4. *Spirochaetal infiltration zone:* Tissue elements appear well preserved but are infiltrated by spirochaetes, both large and intermediate in size. No other bacteria are observed.

Differential diagnosis

- Herpetic gingivostomatitis
- Desquamative gingivitis
- Aphthous stomatitis

Prognosis and predictive factors

- The patient is asked to rinse the mouth for every 2 hours with a mixture of warm water and 3% hydrogen peroxide.
- Penicillin V 250 or 500 mg, 6 hourly and erythromycin 250 or 500 mg, 6 hourly with metronidazole 400 mg, 8 hourly for 7 days are the drugs of choice.

- Additionally, copious fluid consumption and administration of nutritional supplements are advised.

Plasma cell gingivitis

(Synonyms: Plasma cell gingivostomatitis; atypical gingivitis)
It is allergic in origin and caused by some ingredients in chewing gum, dentifrices, various diet compounds such as pepper used for cooking.

Clinical features

- **Age.** Any age group.
- **Gender.** Female predilection.
- **Location.** Oral aspect of attached gingiva.
- **Signs and symptoms**
 - The entire free and attached gingiva is erythematous, friable, granular, bright red and bleeds on slight provocation.
 - Symptoms such as sore and burning of mouth, scaling of lips and angular cheilitis are commonly seen.

Histopathology

- Plasma cell gingivitis demonstrates psoriasiform hyperplasia and spongiosis of surface epithelium with intense exocytosis and neutrophilic microabscess.
- The underlying lamina propria contains numerous dilated vascular channels and an extremely dense chronic inflammatory infiltrate that is composed predominantly of plasma cells.

Prognosis and predictive factors

- Cessation of exposure to allergen resolves the lesion.
- In cases where the allergen is not discovered, they are treated with topical or systemic immunosuppressive medications.

Desquamative gingivitis

(Synonym: Gingivosis)
Desquamative gingivitis is not a disease entity but a clinical term applied to the gingival manifestations of different diseases. It is the term used to describe gingival epithelium that spontaneously sloughs or can be removed

with minor manipulation.

Pathogenesis

McCarthy and his colleagues have proposed a classification of desquamative gingivitis based on aetiology. They have suggested the causative factors to be:

- Certain dermatoses
- Hormonal influences
- Abnormal responses to irritation
- Chronic infections
- Idiopathic

The most important dermatoses presenting gingival involvement categorized as a desquamative gingivitis are:

- Cicatricial pemphigoid (benign mucous membrane pemphigoid)
- Pemphigus vulgaris
- Lichen planus
- Epidermolysis bullosa
- Systemic lupus erythematosus
- Linear IgA disease

Clinical features

- **Age.** >40 years.
- **Gender.** Female predilection.
- **Location.** Buccal and labial portion of gingiva.
- **Signs and symptoms**
 - The gingiva is red, oedematous, glazed and shows areas of superficial ulceration or desquamation of varying extent. Vesicles, bullae, white flecks and striae may also be seen.
 - If blisters are present, they are filled with clear fluid or can be contaminated with blood.
 - Manipulation of the affected erythematous surface epithelium with cotton swab or gauze pad can cause desquamation.
 - Yellowish fibrinopurulent membrane covered areas of frank erosion and significant pain is usually present.

Histopathology

The histopathologic features and immunofluorescent findings of desquamative gingivitis are variable, although most patients report

diagnostic features of lichen planus or pemphigoid.

Prognosis and predictive factors

- A course of doxycycline monohydrate can be prescribed to reduce the degree of mucosal inflammation before immunosuppressive therapy.
- Topical corticosteroid can be applied in patient's resistant to corticosteroid often respond to dapsone or sulphapyridine.

Gingival abscess

Gingival abscess is an acute, localized and painful lesion of sudden onset.

Pathogenesis

It results from bacteria carried deep into the tissue, when a foreign substance is forcefully embedded into the gingiva.

Clinical features

- It is a localized, painful, rapidly expanding lesion that is usually of sudden onset.
- It is limited to the marginal gingiva or interdental papilla.
- During onset, it appears as a red swelling with a smooth, shiny surface.
- Within 24–48 hours, the lesion usually becomes fluctuant and pointed with a surface orifice from which an exudate may be expelled out.

Histopathology

- It consists of a purulent focus in the connective tissue surrounded by a diffuse infiltration of polymorphonuclear leukocytes, oedematous tissue and vascular engorgement.
- The overlying epithelium exhibits secondary changes in the form of intra- and intercellular oedema, microabscess formation and sometimes ulceration.

Prognosis and predictive factors

- Spontaneous rupture is common.
- The invading foreign material, if any, is usually expelled along with the pus.
- Incision and drainage of pus accumulation under local anaesthesia is

advised.

Pericoronitis

Pericoronitis is an inflammation of soft tissues around the crown of an impacted or partially erupted tooth and is seen commonly in association with mandibular third molars.

Pathogenesis

- The space between the crown of the tooth and the overlying mucosal flap is an ideal area for the accumulation of bacterial plaque and food debris, which leads to inflammation.
- Inflammatory oedema leads to swelling of the flap which predisposes to trauma from the opposing teeth and exacerbation of the inflammation.

Clinical features

- **Age.** Adult age group.
- **Gender.** No sex predilection.
- **Location.** Mandibular third molars.
- **Signs and symptoms**
 - The usual symptoms are pain, tenderness in the gum flap and a bad taste, which is associated with persistent oozing of pus from beneath the flap.
 - Limitation of opening and discomfort on swallowing may also be present.
 - Patient may have mild fever, malaise and regional lymphadenopathy.
 - In severe cases, an acute pericoronal abscess may develop which can remain localized or be associated with cellulitis and extension of infection into adjacent surgical spaces.

Histopathology

- The epithelium of the pericoronal flap shows hyperplasia, intercellular oedema and leukocytic infiltration.
- The underlying connective tissue exhibits increased vascularity, dense diffused infiltration with lymphocytes and plasma cells along with varying number of polymorphonuclear leukocytes.

Prognosis and predictive factors

- Acute pericoronitis is treated with antiseptic lavage under the gingival flap to remove food debris and bacteria.
- Systemic antibiotics are used to reduce fever.
- Once the acute phase has subsided, the tooth can be extracted. If tooth retention is desirable, the overlying gingival flap is surgically removed.

Gingival enlargements

Gingival enlargements can be classified based on aetiologic factors and pathologic changes as follows:

- Inflammatory gingival enlargement:
 - Acute
 - Chronic
- Drug-related gingival hyperplasia
- Enlargement associated with systemic factors:
 - Conditioned enlargement
 - Enlargements due to systemic diseases
- Neoplastic enlargements
- Idiopathic gingival enlargement
- False gingival enlargement

Inflammatory gingival enlargement

1. Acute inflammatory gingival enlargement

It results from bacteria carried deep into the tissues, when a foreign substance is forcefully embedded into the gingiva.

Clinical features

- It is a localized, painful, rapidly expanding lesion that is usually of sudden onset.
- It is limited to the marginal gingiva or interdental papilla.
- During onset, it appears as a red swelling with a smooth, shiny surface. Within 24–48 hours, the lesion usually becomes fluctuant and pointed with a surface orifice, from which an exudate may be expressed.

Histopathology

It consists of a purulent focus in the connective tissue, surrounded by a diffuse infiltration of polymorphonuclear leukocytes, oedematous tissue and vascular engorgement.

Prognosis and predictive factors

Incision and drainage under local anaesthesia is done.

2. Chronic inflammatory enlargement

It occurs due to prolonged irritation of the gingival tissue such as poor oral hygiene, accumulation of dental calculus, abnormal relationship of adjacent and opposing tooth, over-hanging restoration and habit such as mouth breathing.

Clinical features

- It originates as a sight ballooning of the interdental papilla or marginal gingiva.
- In early stages, it produces bulge around the involved teeth and increases in size, until it covers a part of the crown.
- Lesion may be deep red or bluish red in colour. They are soft and friable with smooth shiny surface, which shows tendency to bleed.
- Sometimes, enlargement can occur as discrete, sessile or pedunculated mass. They may undergo spontaneous reduction in size followed by exacerbation and continued enlargement.

Histopathology

- A proliferative feature of chronic inflammation is seen.
- Lesion may contain preponderance of mixed inflammatory cells with vascular engorgement.

Prognosis and predictive factors

- Removal of aetiological factors.
- Antibiotic course is given.
- If necessary, flap surgery is done.

Drug-related gingival hyperplasia

- Drug-related gingival hyperplasia refers to an abnormal growth of the

gingival tissues secondary to use of a systemic medication. The degree of gingival enlargement appears to be related to the patient's susceptibility and the level of oral hygiene.

- The term is a misnomer because neither the epithelium nor the cells within the connective tissue exhibit either hyperplasia or hypertrophy. The increased gingival size is due to an increased amount of extracellular matrix, predominantly collagen. Therefore, several authors designate the alteration as *medication-associated gingival enlargement or gingival overgrowth*.
- A list of medication reported with gingival hyperplasia is provided.
 1. **Anticonvulsants**
 - Carbamazepine
 - Ethosuximide
 - Ethotoin
 - Felbamate
 - Mephenytoin
 - Methsuximide
 - Phenobarbital
 - Phensuximide
 - Phenytoin
 - Primidone
 - Sodium valproate
 2. **Calcium channel blockers**
 - Amlodipine
 - Bepridil
 - Diltiazem
 - Felodipine
 - Nicardipine
 - Nifedipine
 - Nimodipine
 - Nitrendipine
 - Verapamil
 3. **Cyclosporine**
 4. **Erythromycin**
 5. **Oral contraceptives**

Clinical features

- The gingival enlargement due to phenytoin is mostly seen in people

younger than 25 years.

- The gingival enlargement due to calcium channel blockers occurs mainly in middle aged or older adults.
- Cyclosporine is used over a broad age range and this correlates with age of reported hyperplasia.
- After 1–3 months of drug use, the enlargements originate in the interdental papillae and spread across the tooth surfaces. The anterior and facial segments are the most frequently involved areas.
- In the absence of inflammation, the enlarged gingiva is normal in colour and firm in consistency, with smooth, stippled or granular surface.
- With inflammation, the affected gingiva often becomes dark red and oedematous, with a surface that is friable, bleeds easily and is occasionally seen in the presence of heavy inflammation.

Histopathological features

- Hyperplastic gingival tissues removed from lesions caused by phenytoin or the dihydropyridines reveal redundant tissue of apparently normal composition.
- Cases related to cyclosporine use demonstrate increased amount of collagen, with normal density of fibroblasts.
- The overlying surface epithelium may demonstrate elongation of rete ridges, with long extensions into the underlying lamina propria.
- With secondary inflammation, there is increased vascularity and a chronic inflammatory cellular infiltrate that most frequently consists of lymphocytes and plasma cells.

Prognosis and predictive factors

- Discontinuation of the offending medication by attending physician often results in cessation and possibly some regression of the gingival enlargement.
- Eradication of the excess gingival tissue is achieved by gingivectomy.

Enlargement associated with systemic factors

Conditioned enlargement

Conditioned enlargements are caused by the systemic condition of the patient, which exaggerates the usual gingival response to dental plaque.

However, bacterial plaque is essential for the initiation of this type of enlargement. There are three types of conditioned enlargements: (i) hormonal, (ii) nutritional and (iii) allergic.

Hormonal enlargement

- Gingival enlargement often occurs at puberty, in both men and women.
- Some authors believe that it occurs due to endocrine imbalance at this particular stage of the patient's development.
- Others believe that it may occur because of poor oral care, local irritation associated with eruption of teeth and/or inadequate nutrition.
- It may also occur during pregnancy. This proliferation may be due to disturbed nutrition, poor oral hygiene or some systemic predisposition towards proliferation. Increased levels of oestrogen and progesterone in pregnancy cause change in the vascular permeability, which leads to gingival oedema and altered inflammatory response to dental plaque.
- Microscopic studies of these gingival lesions reveal increased vascularity, multiplication of fibroblasts, oedema and infiltration of leukocytes into the gingiva.

Nutritional enlargement

Vitamin C deficiency

- The spongy, bleeding gums of scurvy (vitamin C deficiency) have been recognized as a specific entity.
- The enlargement of gingiva is generally included in the classic description of scurvy.
- This enlargement is essentially a conditioned response to bacterial plaque.
- The combined effect of vitamin C deficiency and inflammation produces this enlargement.
- The gingiva becomes tender, swollen and oedematous. It bleeds upon the slightest provocation.
- Gingival sulci are often filled with clotted blood and the crests of the interdental papillae are red or purple.
- Sometimes, ulceration and necrosis of the interdental papillae is seen as infection becomes superimposed upon the susceptible tissues.
- Treatment: It includes improvement of oral hygiene and administration of vitamin C.

Allergic enlargement

Plasma cell gingivitis.

It is already explained on page 241.

Enlargement due to systemic diseases

1. Leukaemia

Explained in Chapter 18 Diseases of the Blood and Blood Forming Organs.

2. Granulomatous diseases

Granulomatous diseases may involve the gingiva and present as gingival enlargement. Common diseases in which gingiva is involved are Crohn's disease, sarcoidosis, Wegener's granulomatosis and foreign body gingivitis.

3. Crohn's disease

(Synonym: Regional enteritis)

- Crohn's disease is a slowly progressive disease of unknown aetiology.
- It may be an unusual reaction to an extrinsic agent, possibly of infective origin.
- Atypical mycobacteria have been implicated in some cases.
- It occurs in individual of all ages, involves both genders equally and is characterized by granulomatous, superficial ulcerations of intestinal tract with frequent fistulas developing on to body surfaces or viscera or between intestinal loops.
- The most commonly involved areas are the buccal mucosa, where the lesions present a cobblestone appearance; the vestibule, where linear and hyperplastic folds, which may mimic denture-induced hyperplasia; the lips, which appear diffusely swollen and indurated; the gingiva and alveolar mucosa, which exhibit a granular erythematous swelling; and the palate, where multiple ulcers occur.
- Glossitis may be seen secondary to malabsorption of vitamin B_{12}.
- The oral lesions may either precede or follow the appearance of the intestinal lesions, and like those lesions, commonly show periods of quiescence alternating with exacerbations of the process.
- The microscopic findings of lesions are those of a chronic granulomatous disease. Microscopically, it consists of fibrosis and a focal dense collection of lymphocytes and plasma cells. Lymph vessels appear dilated. The

presence of non-caseating granuloma which is typically small, consisting of macrophages, epithelioid cells and occasional giant is seen.

Prognosis and predictive factors

- Oral lesions resolve when intestinal disease is controlled.
- The use of oral sulphasalazine or intralesional injection of corticosteroid gives good results.

Idiopathic gingival enlargement

(Synonyms: Fibromatosis; fibromatosis gingivae; elephantiasis gingivae; congenital macrogingiva)

- This enlargement may be detected at an early age and in few cases even at birth.
- The cause of this developmental enlargement of gingival tissue is unknown. It is probably hereditary, being transmitted as an autosomal dominant trait in some instances.
- In some cases, the gingival tissues are so diffusely enlarged that the teeth are also diffusely covered.
- If the enlargement is present before tooth eruption, the dense fibrous tissue may even interfere with or prevent eruption.
- It presents as large masses of firm, dense, resilient, insensitive growth that covers the alveolar ridges and extends over the teeth. It is normal in colour and the patient complains only of the deformity.

Histopathology

- It shows hyperplastic epithelium with elongation of rete ridges and mild hyperkeratosis.
- The underlying connective stroma is made up of dense bundles of mature fibrous tissue with few young fibroblasts.
- Occasionally, few chronic inflammatory cells are seen.

Neoplastic enlargements are due to benign and malignant neoplasms involving the gingiva, it is discussed in Chapter 2 Benign and Malignant Tumours of the Oral Cavity.

False enlargements occur due to underlying dental or osseous anomalies and are not an actual abnormality of the gingiva.

Periodontitis

Classification of periodontitis

Periodontitis is classified as follows:

- Chronic periodontitis
 - Localized
 - Generalized
- Aggressive periodontitis
 - Localized
 - Generalized
- Periodontitis as a manifestation of systemic diseases
 - Associated with haematologic disorders
 - Associated with genetic disorders
 - Not otherwise specified
- Necrotizing periodontal diseases
 - Necrotizing ulcerative gingivitis (NUG)
 - Necrotizing ulcerative periodontitis (NUP)
- Abscess of the periodontium
 - Gingival abscess
 - Periodontal abscess
 - Pericoronal abscess
- Periodontitis associated with endodontic lesions

Chronic periodontitis

It is most common and prevalent in adults but can also be observed in children. It is generally a slow form of periodontitis which undergoes acute exacerbation with the attachment loss.

Pathogenesis

- Microbial plaque, calculus, food impactions and irritating margins of fillings are important factors responsible for periodontitis.
- Chronic periodontitis is predominantly associated with *Actinobacillus actinomycetemcomitans, Bacteroides forsythus, Porphyromonas gingivalis* and *Prevotella intermedia.*
- *Smoking:* There is a considerable body of evidence that tobacco smoking is an important risk factor for the development and progression of

periodontal disease. The mechanism is not fully understood but smoking impairs the phagocytic function of polymorphoneutrophils (PMNs) and impairs healing. The composition of subgingival plaque may also affect and favour the potential overgrowth.

- Drugs: Drugs which affect inflammatory and immune responses, such as immunosuppressants and non-steroidal anti-inflammatory agents, might be expected to influence the course of periodontal disease by modifying the response of the host to products from microbial plaque.
- Nutrition: The relationship between nutrition and periodontal disease is controversial except in rare cases of gross deficiency states.
- Diabetes mellitus: The relationship between diabetes and periodontal disease is unclear. Although it is commonly held that the periodontal disease is more severe and progresses faster in both type I and II diabetic patients than in non-diabetics. Vascular changes and defects in cellular defence mechanism have been suggested as possible ways in which diabetes could increase susceptibility to periodontal disease.

Clinical features

- The clinical features are gingival inflammation, bleeding on probing, reduced resistance of the periodontal tissues to probing, loss of clinical attachment and alveolar bone.
- Variable features include gingival enlargement, recession of gingiva, furcation involvement, increased tooth mobility, drifting of teeth and eventually exfoliation of teeth.

Radiographic features

- The earliest change in the periodontal bone is a blunting of the alveolar crest due to the beginning of bone resorption.
- Horizontal bone loss is predominantly seen.
- Increased periodontal space width is seen.

Histopathological features

- The enlarged free marginal gingiva is densely infiltrated with lymphocytes and plasma cells.
- The apical borders of the inflamed area approach the crest of alveolar bone and the crestalfibres of the periodontal ligament.
- The early microscopic signs of the encroachment of the inflammatory

process on the periodontium are the appearance of the giant cells (osteoclasts) with Howship's lacunae on the surface of the bone.

- As the disease progresses,
 - the epithelial attachment proliferates apically on to the cementum of the tooth and shows more ulceration.
 - the alveolar crest of bone is resorbed further apically.
 - principally, periodontal ligament fibres become disorganized and detached from the tooth.
 - a periodontal pocket descends down, until finally the apex of the tooth approached.
- The vicious cycle of irritant collection, inflammation and detachment continues along with periodontal bone resorption in an apical direction.

Prognosis and predictive factors

- Complete oral prophylaxis, which includes scaling and curettage.
- Flap surgery is the ideal treatment of choice.

Aggressive periodontitis

(Synonyms: Juvenile periodontitis; rapidly progressive periodontitis)
Aggressive periodontitis is a rapidly progressing type of periodontitis that occurs in patients who do not have large accumulation of plaque and calculus. This may be either localized or generalized form.

Pathogenesis

- The aetiology and pathogenesis of the condition remain obscure. The lesions are inflammatory and bacterial plaque is the prime aetiological factor, but the degree of destruction does not commensurate with the generally small amounts of plaque present.
- Aggressive periodontitis is dominated by gram-negative anaerobic rods, particularly *Actinobacillus actinomycetemcomitans.*
- It has a familial tendency suggesting a genetic predisposition.
- Abnormalities in cell-mediated immunity and in neutrophils function have also been demonstrated.

Clinical features

- **Localized aggressive periodontitis**

- Circumpubertal onset.
- Localized first molar or incisor presentation with interproximal attachment loss affecting at least two permanent teeth, one of which is first premolar and involving no more than first molars and incisors.
- Robust serum antibody response to infecting agents.

- **Generalized aggressive periodontitis**
 - It usually affects individuals under 30 years of age.
 - Generalized interproximal attachment loss affecting at least three permanent teeth other than first molar and incisors.
 - Pronounced episodic nature of the destruction of attachment and alveolar bone.
 - Poor serum antibody response to infecting agents.
- The disease is characterized by rapid destruction of alveolar bone with vertical bone loss resulting in deep infrabony pockets.
- Gingiva is acutely inflamed, often proliferated, ulcerated and appears fiery red.
- Some patients may have systemic manifestation such as weight loss, mental depression and general malaise.

Radiographic features

- In localized form, vertical loss of alveolar bone is seen around the first molar and incisors. An arc-shaped alveolar bone loss extends from the distal surface of the second premolar to the mesial surface of the second molar and there is widening of the periodontal ligament space.
- In generalized form, bone loss may range from the involvement of one or two teeth to a maximum number of teeth.

Note: In aggressive periodontitis, vertical bone loss is predominantly seen, whereas horizontal bone loss is seen in chronic periodontitis.

Histopathology

It closely resembles the features of chronic periodontitis.

Prognosis and predictive factors

- If microflora contains gram-positive microorganisms, then it is treated

with 250 mg amoxicillin and 125 mg potassium clavulanate three times daily for 14 days, along with scaling and root planning.
- If flora is gram-negative, then 150 mg clindamycin is given four times a day for 7 days, along with scaling and root planning.

Papillon–Lefévre syndrome

- It is an autosomal recessive and inherited disorder.
- It is a triad of hyperkeratosis of palms and soles, extensive prepubertal destruction of periodontal bone supporting the dentition with extensive generalized horizontal bone loss and calcification of dura.

Clinical features

- It usually begins after eruption of the primary second molar.
- Gingival inflammation and horizontal bone destruction are present.
- Loss of primary dentition at the age of 5 years and loss of secondary dentition at the age of 20 years.
- Gingival swelling and severe halitosis are present.
- Mastication is often difficult and painful.

Histopathology

- Histopathologic features resemble chronic periodontitis and are not specific.
- Crevicular epithelium shows hyperplastia and exocytosis.
- The underlying connective tissue exhibits increased vascularity and a mixed inflammatory cellular infiltrate consisting predominantly of PMN cells, lymphocytes, histiocytes and plasma cells.
- The lateral walls of the periodontal pocket show predominant osteoclastic activity and apparent lack of osteoblastic activity.

Prognosis and predictive factors

Oral prophylaxis and flap surgery are indicated.

Necrotizing ulcerative periodontitis

- It occurs after repeated long-term episodes of necrotizing ulcerative gingivitis.
- It is commonly associated with AIDS.

- Inflammatory infiltrate in the lesions of acute necrotizing ulcerative gingivitis (ANUG) can extend to the underlying bone, resulting in deep crater-like osseous lesion, which is most often located in the interdental area.

Clinical features

- It is commonly accompanied by fever, malaise and lymphadenopathy.
- Initially, necrotizing ulcerative gingivitis is seen.
- It shows rapid generalized loss of attachment and bone.
- Deep conventional pockets are not found because the ulcerative and necrotizing characters of the gingival lesion destroy the junctional epithelium removing the mechanism of pocket deepening.

Prognosis and predictive factors

- As the patient has underlying predisposing factors, it should be treated in consultation with a physician.
- Topical and systemic antimicrobials should be given, based on the result of laboratory test.

Lateral periodontal abscess

The lateral periodontal abscess is a localized area of suppurative inflammation arising within the periodontal tissues alongside a tooth and is distinct from the more common periapical abscess.

Pathogenesis

- It commonly arises in patients with pre-existing advanced periodontitis or may occur either as a direct result of an increase in virulence and toxic factors released by plaque organisms or secondary to reduction in host resistance.
- Obstruction to the drainage of exudate from a pocket predisposes to abscess formation. This may occur particularly in infrabony pockets pursuing a tortuous course around the root or where fibrosis or oedema in the superficial parts of the pocket causes tight approximation of the soft-tissue wall to the neck of the tooth.
- Impaction of foreign material, such as food debris, into a pocket may also lead to abscess formation.

- In the absence of pocket, periodontal abscess may follow traumatic injury to a tooth, lateral perforation of the root in endodontic therapy or stab infections. The later arise when a foreign object, such as a tooth brush bristle or sharp food particles, penetrates the tissue introducing infection into the periodontal ligament. If there is only superficial penetration, the abscess will be located in the gingiva.

Clinical features

- Clinically, periodontal abscesses may be acute or chronic.
- An acute abscess develops rapidly and is accompanied by throbbing pain and redness, swelling and tenderness of the overlying mucosa.
- The affected tooth is usually tender to percussion but most are vital.
- The abscess may discharge spontaneously through the opening of a pocket, but in deep-seated lesions or where drainage is obstructed, it may track and present with a sinus opening on the mucosa somewhere along the length of the root.
- Discharge of pus relieves the acute symptoms and the lesion may heal or become chronic with intermittent discharge.
- The chronic abscess may be asymptomatic or give rise to episodes of dull pain. Acute exacerbations are common.

Histopathology

- Microscopically, the abscess resembles an abscess elsewhere.
- It consists of a central cavity filled with pus walled off on one side by the root of the tooth and on the other connective tissue; because it is likely that in most instances, the epithelial lining of the crevice would have been destroyed by the inflammatory process.

Prognosis and predictive factors

- A direct incision, perpendicular to the long axis of the involved tooth, releases pus.
- If the abscess does not drain spontaneously through the gingival crevice and if it is not treated, a fistula may develop to release the pus spontaneously on to the mucosal surface.
- Careful insertion of a dull probe into the pocket along the tooth will usually induce drainage and acute symptoms will subside.
- The abscess will recur unless the cause is removed and the depth of the

pocket is reduced.

Periodontitis associated with endodontic lesions are discussed in Chapter 9 Diseases of Dental Pulp and Periapical Tissues.

Key points

- *Gingivitis:* Inflammation of the gingiva.
- *NUG* is caused by *Fusiform bacilli* and *Borrelia vincentii.*
- *Four zones* associated with gingival lesion of NUG are bacterial zone, neutrophil-rich zone, necrotic zone, spirochaetal infiltration zone.
- *Plasma cell gingivitis* is an allergic lesion due to some ingredients in chewing gum, dentifrices and various diet compounds.
- *Desquamative gingivitis:* Cicatricial pemphigoid, pemphigus vulgaris, lichen planus, epidermolysis bullosa, systemic lupus erythematosus and linear IgA disease.
- *Pericoronitis* is an inflammation of soft tissues around the crown of an impacted or partially erupted tooth, usually third molar.
- *Drug-induced gingival hyperplasia* is caused by anti-convulsants (carbamazepine, phenytoin, sodium valproate), calcium channel blockers (amlodipine, nifedipine, verapamil), cyclosporine and few oral contraceptives.
- *Crohn's disease* is characterized by granulomatous, superficial ulcerations of intestinal tract with frequent fistulae developing onto body surfaces or viscera, or between intestinal loops.
- *Aggressive periodontitis* is caused by gram-negative anaerobic rods, particularly *Actinobacillus actinomycetemcomitans*.
- *Papillon–Lefévre syndrome* is a triad of hyperkeratosis of palms and soles, extensive prepubertal destruction of alveolar bone and calcification of dura.

Frequently asked questions

1. Classify periodontal diseases. Write about pathogenesis, clinical features and histopathology of gingivitis.
2. Necrotizing ulcerative gingivitis.
3. Pericoronitis.
4. Drug-induced gingival enlargement.
5. Aggressive periodontitis.

6. Papillon–Lefévre syndrome.

CHAPTER 8

Dental caries

Definition

- Dental caries can be defined as a progressive, posteruptive, microbial disease affecting dental hard tissues resulting in demineralization of the inorganic constituents and dissolution of the organic components, which often lead to cavitation.
- It is a dynamic process where both demineralization and remineralization occur simultaneously.
- When the rate of demineralization exceeds the rate of remineralization, then there is frank cavity formation.
- *Caries* is Latin for *rot* or *rotten*. In Greek, *ker* means *death.*
- Dental caries is formed by a complex interaction of cariogenic diet, acidogenic microorganisms and a susceptible host over a period of time. Various factors influence the initiation and progression of disease.

Theories of dental caries

The legend of worm

- The earliest reference to dental caries is found in ancient Sumerian textbook known as *Legends of Worms* that dates back to 5000 BC.
- Concept: The caries is caused by worms and is the cause for toothache (Homer).

Endogenous theory (humoral theory)

- It was advocated by Greek physicians.
- Concept: The dental caries is produced by internal action of acids and corroding humors and whose imbalance results in disease.

Chemical theory or acid theory

- It was instituted by Parmly in 1820.
- Concept: An unidentified chymal agent is responsible for caries.
- According to this theory, teeth are destroyed by the acids formed in the oral cavity by the putrefaction of protein which produces ammonia and is

subsequently oxidized to nitric acid.

- Later it was supported by Robertson in 1835, who proposed that dental decay is caused by acid forms by fermentation of food particles around the tooth.

Parasitic or septic theory

- Concept: It is stated that microorganisms can have toxic and destructive effects on dental tissues.
- Ficinus, a dental physician, implied that filamentous microorganisms (denticolae) in the enamel cuticle and in carious lesions cause decomposition of the enamel and dentine.

Miller's chemoparasitic theory or acidogenic theory

- Willoughby D Miller proposed this theory in 1882.
- Concept: Dental caries is caused by acids produced by microorganisms of mouth.
- Dental decay is a chemicoparasitic process consisting of two stages: (i) the decalcification of enamel which results in its total destruction and (ii) the decalcification of dentine as a preliminary stage, followed by dissolution of the softened residue. In case of enamel, however, the second stage is practically wanting, the decalcification of enamel signifying its total destruction.
- Based on his experimental studies on both microorganism and acids, Miller observed that three essential factors are necessary for dental caries:
 1. Carbohydrate substrate
 2. Oral microorganisms
 3. Acid, which causes dissolution of tooth minerals.

Role of carbohydrate in dental caries

- The presence of readily fermentable carbohydrates has been thought to be responsible for their loss of caries resistance.
- The cariogenic carbohydrates are dietary in origin, since uncontaminated human saliva contains negligible amounts of carbohydrate regardless of the blood sugar level.
- Salivary carbohydrates are bound to proteins and other compounds and are not readily available for microbial degradation.
- The cariogenicity of dietary carbohydrates varies with the frequency of

ingestion, physical form and chemical composition, route of administration and presence of other food constituents.

- Sticky, solid carbohydrates are more cariogenic than those consumed as liquids.
- Carbohydrates which are readily cleared from oral cavity by saliva and swallowing are less conducive to caries than those which are slowly cleared.
- Polysaccharides are less easily fermented by plaque bacteria than monosaccharides and disaccharides. Plaque organisms produce little acid from the sugar alcohols, sorbitol, xylitol and mannitol. This also implies that all carbohydrates are not cariogenic.
- Carbohydrates fed through stomach tube or intravenously do not contribute to decay as they are unavailable for microbial breakdown.
- Food with high fat, carbohydrates, protein or salt reduces the oral retentiveness of carbohydrates.

Role of microorganisms in dental caries/microbiology of dental caries

- Miller demonstrated the presence of microorganisms within the tubules of decayed teeth mainly cocci and leptothrix, and laid the foundation for the role of acids elaborated by bacteria in caries production.
- Evidence showing the role of bacteria in dental caries:
 - Germ-free animals do not develop dental caries
 - Antibiotics administrated to animals result in reducing the incidence of dental caries
 - Unerupted teeth do not develop dental caries
 - Microorganisms have been isolated from enamel and dental caries
- Several organisms are capable of inducing carious lesion. It includes: *Streptococcus mutans, S. sanguis, S. mitior, S. salivarius, S. milleri, Peptostreptococcus intermedius, Actinomyces israelii, A. naeslundii, Lactobacillus acidophilus* and *L. casei.*
- Few organisms such as *L. fermentum* and *S. lactis* do not induce dental caries, suggesting that *not all microorganisms cause dental caries*.
- Different microorganisms display certain selectivity for the tooth surface, where they localize and attack the tooth structures (Table 8.1).

Table 8.1

Localization of microflora related to caries in animal models

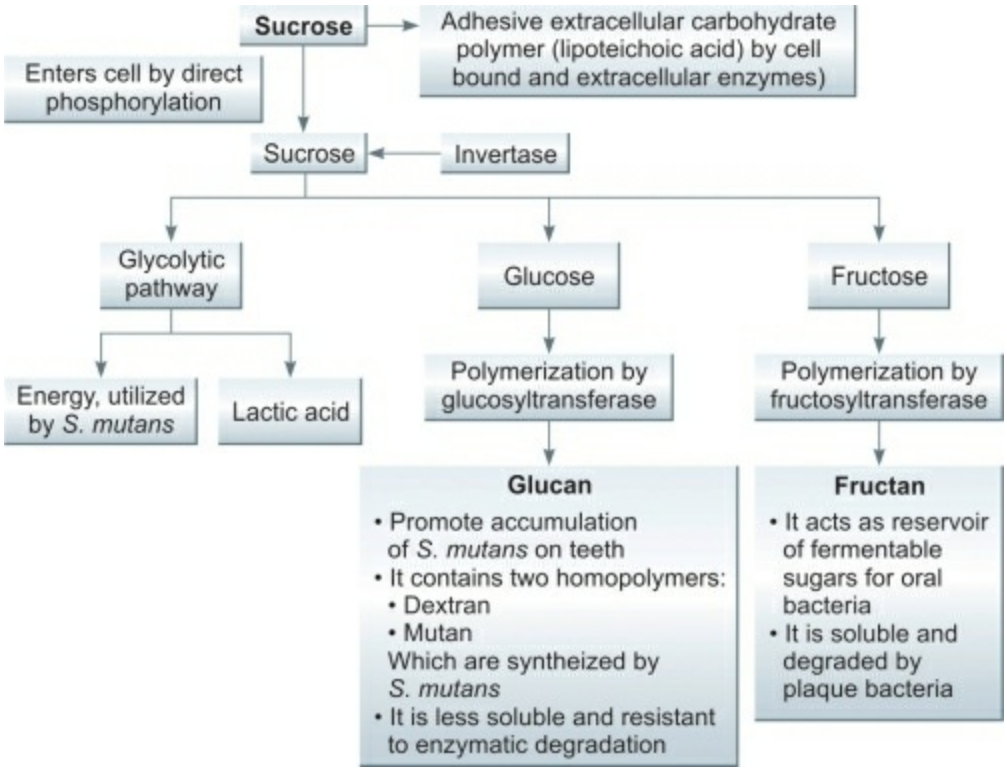
Type of caries	Microorganisms	Human disease
Pit and fissure	*S. mutans* *S. sanguis* *Lactobacillus species* *Actinomyces species*	Very significant Uncertain Very significant By chance
Smooth surface	*S. mutans* *S. salivarius*	Very significant By chance
Root surface	*A. viscosus* *A. naeslundii* *S. mutans* *S. sanguis*	Very significant Very significant Significant By chance
Deep dental caries	*Lactobacillus sp.* *A. naeslundii* Other filamentous rods	Very significant Very significant Very significant

Oral streptococci

The important species found in the oral cavity includes *S. mutans, S. sanguis, S. mitior, S. salivarius* and *S. milleri.*

1. S. mutans

- It was first isolated by Clarke in 1924.
- It is catalase-negative, gram-positive cocci forming short to medium chains.
- *S. mutans* synthesizes insoluble polysaccharides from sucrose. It is homofermentative and is more aciduric than other oral streptococci.
- In the oral cavity, *S. mutans* does not colonize in the mouth of infants prior to the eruption of teeth. Likewise, it disappears from the mouth following the extraction of all teeth.
- It is more aciduric and acidogenic than other oral streptococci species.
- *S. mutans* forms a homogenous group based on several phenotypic characteristics. However, based on nucleic acid–base content and hybridization, *S. mutans* has been divided into five genotypes: (i) *S. mutans*, (ii) *S. rattus*, (iii) *S. sobrinus*, (iv) *S. cricetus* and (v) *S. ferus.* Among all these species, *S. mutans* and *S. sobrinus* are most commonly found in human dental plaque.
- *Metabolism of S. mutans:* Metabolism of *S. mutans* is depicted in Flowchart 8.1.



FLOWCHART 8.1 Metabolism of *S. mutans*

S. sanguis, S. mitior, S. salivarius, S. milleri and *Peptostreptococcus intermedius* are less cariogenic bacteria.

2. Actinomyces

- These are gram-positive, filamentous organisms.
- These include *A. naeslundii* and *A. viscosus,* which are facultative anaerobes and *A. israelii* and *A. odontolyticus,* which are strict anaerobes.
 - *A. viscosus* is an acidogenic bacterium, which contains intracellular polysaccharide stores and also forms extracellular levans and heteropolysaccharides consisting of hexosamine and hexose. It is a predominant flora of plaque overlying root lesions.
 - *A. israelii, A. naesulandii* and *A. odontolyticus* are less cariogenic bacteria.

3. Lactobacilli

- These are gram-positive, nonspore-forming rods that grow under microaerophilic conditions.
- *L. casei* and *L. acidophilus* are the most common species involved in dental caries.
- These are acidophilic and acidogenic and could therefore multiply in the low pH of plaque and carious lesions. Lactobacilli are a universal etiologic

agent in dental caries; however, their role is questioned because the amount of acid formed by lactobacilli present in plaque is insignificant in comparison to that produced by other acidogenic oral organisms.

- *These may be 'secondary' invaders.* This possibility is supported by the observations that lactobacilli are not detectable in plaque covering white spot lesions on smooth surfaces and their predominant site of attack being deep fissures and in deep dentinal lesions favouring their retention.

4. veillonella

- These are gram-negative cocci commonly found in plaque.
- These are possibly anticariogenic bacteria. These microorganisms lack key enzymes involved in glycolysis and the hexose monophosphate shunt and therefore, do not utilize sugars as an energy source.
- These utilize lactic acid (pKa 3.08) by converting it into propionic and other weak acids (pKa 4.7).

Role of acids in dental caries

- The acids in the oral cavity are produced through enzymatic breakdown of the carbohydrates by bacteria and the acid formed is chiefly *lactic acid*.
- The mere presence of acid in the oral cavity is not sufficient unless it localizes upon the tooth surface for a period of time. This suggests a mechanism for holding acids at a given area for relatively long period of time. It is generally agreed that dental plaque fulfils this function.
- Generally, monosaccharides and disaccharides result in the greatest fall in plaque pH due to more production of acids.
- The acid formation is slower upon application of cooked starch, possibly due to slower diffusion of larger starch molecules and acid production that occurs from the comparatively low concentration of maltose released from starch.
- Each glycolysis cycle in plaque forms two molecules of lactic acid from one molecule of glucose.
- Organisms such as streptococci and lactobacilli ferment sugars to produce 90% or more lactic acid as the end product, and are called *homofermentive.*

Heterofermentives produce a mixture of metabolites including other organic acids such as propionic acid, butyric acid, succinic acid and ethanol.

- In anaerobic conditions, *Actinomyces* are homolactic but in the presence of oxygen, the fermentation is heterolactic with formate, acetate, lactate and

succinate as their products.

- In caries active individuals, the pH at the tooth surface remains below the critical pH of 5.5, for 20 to 50 minutes following a single exposure to sucrose. Moreover, it is very important that repeated intakes of sweets in between the meals can result in an almost continuous acid attack on the tooth surfaces.
- Below the critical pH of 5.5, the tooth minerals act as buffers. This type of buffering activity initially helps to maintain the local pH at nearly 5.5.
- However, when the local pH falls to about 5.0, subsurface demineralization is inevitable in the enamel, which results in the formation of incipient caries, where the surface of the enamel is intact but it has started to demineralize deep and below the surface enamel, the process is known as *subsurface demineralization*.
- When the pH is lowered further and it goes to the level of about 3.0–4.0, the surface of the enamel begins to get etched and resorbed. The repeated acid attacks due to prolonged and continuous fall of pH result in cavitations on the tooth surface.
- Limitations of acidogenic theory: The following points are unanswered by Miller's chemoparasitic theory.
 - Why dental caries has predilection to specific sites of a tooth?
 - How dental caries occurs in impacted tooth/erupted tooth?
 - Why some populations are caries free and others are more predilected?
 - The initiation of smooth surface dental caries.
 - The phenomenon of arrested dental caries.

Proteolytic theory (Gottlieb, 1944)

- It was proposed by Gottlieb in 1944.
- Concept: Caries is essentially a proteolytic process, i.e. the microorganisms invade the organic pathways and destroy them in their advance. Acid formation accompanies proteolysis.
- The microorganisms invade in the organic pathways (lamellae, enamel rod sheaths) of the enamel and initiate dental caries through destruction of the organic matrix of enamel by proteolytic action. Subsequently, the inorganic salts are dissolved by acidogenic bacteria.
- The concept of proteolytic theory was further extended by Pincus (1949). He proposed that the sulphatase enzymes liberated by gram-negative bacilli hydrolyze Nasmyth's membrane and other enamel proteins yielding sulphuric acid, which dissolve the mineral portion of the enamel.

- This acid combines with calcium and form calcium sulphate which is demonstrated only in dental caries.
- Limitations of proteolytic theory: No satisfactory evidence to support the claim that the initial attack on enamel is proteolytic, because the organic (protein) content of enamel matrix is very scanty. However, this mechanism can be more appropriate in cases of dentinal and cemental caries.

Proteolysis–Chelation theory (Schatz, 1955)

- It was proposed by Schatz in 1966.
- Concept: Simultaneous microbial degradation of the organic components and the dissolution of the minerals of the tooth by the process known as chelation.
- It considers that, initially during dental caries, proteolytic breakdown of the organic portion of the entire enamel matrix takes place. Following this, a chelating agent is formed by the combination of proteolytic breakdown products, acquired pellicle and food debris, etc. which facilitates tooth decay. The whole process is helped by the bacterial enzymes which facilitate tooth decay.
- The chelating agent, which is formed, is always negatively charged (mostly due to its protein content) and releases the positively charged calcium ions (Ca^{++}) from the enamel or dentine. This process is called *chelation*, and it eventually results in tooth decay. So, *chelation* can be defined as a process that involves the complexing of a metallic ion to a complex substance by a coordinate covalent bond, which results in a highly stable, poorly dissociated and weakly ionized compound called *chelate*.
- This theory explains that the destruction of organic matrix of the enamel as well as its mineral contents both occur simultaneously and interdependently.

Sucrose theory (Egglers-Lura, 1967)

- It was proposed by Egglers-Lura in 1967.
- Concept: Sucrose itself, and not the acid derived from it, can cause dissolution of enamel by forming an ionized calcium saccharate.
- The high concentration of sucrose in the mouth of a caries-active individual may result in the formation of complexes like calcium saccharates and calcium complexing intermediaries by the action of

phosphorylating enzymes. These complexes cause release of the calcium and phosphorus ions from the enamel resulting in tooth decay.

- This theory is unlikely to be significant because once the sucrose is in the oral cavity, it readily gets metabolized to form acids and there is hardly any for formation of calcium saccharates, etc. Moreover, for the formation of calcium saccharate, a very high level of pH is required, the range which is never achieved in the oral cavity.

Autoimmune theory

Concept: Few odontoblast cells, at some specific sites, within the pulp of a few specific teeth, are damaged by autoimmune mechanisms; so, the defence capacity and integrity of the overlying enamel or dentine in those specific areas are compromised, and they can be the potential sites for caries development in future.

Aetiology of dental caries/role of host factors for dental caries

- Dental caries is a multifactorial disease. The primary factors causing dental caries include:
 - The host (tooth surface)
 - The microbial flora (caries causing bacteria)
 - The substrate (sucrose)
 - The time
- The susceptible host, a cariogenic bacterium and suitable substrate like sucrose should be present for sufficient period of time for the development of dental caries.
- The different individuals will be susceptible to different degrees of dental caries depending on the shape of their teeth, their composition and position in the arch, their dietary habits, buffering capacity of saliva and their systemic conditions.

Aetiology of dental caries

Aetiology of dental caries is described in Table 8.2.

Table 8.2

Aetiology of dental caries

Host factors	Components
Tooth	• Composition • Morphologic characteristics • Position
Saliva	• Composition • pH • Quantity • Viscosity • Antibacterial factors
Diet	• Physical factors (quality of diet) • Local factors (carbohydrate, vitamin, fluorine)
Systemic conditions	

Tooth

Composition

- The structure and composition of teeth influence the initiation and the rate of progression of dental caries.
- Brudevold indicated that *surface enamel is more resistant to caries* than subsurface enamel. Surface enamel is more highly mineralized and tends to accumulate greater quantity of fluoride, zinc, lead and iron than underlying enamel. Also, the concentration of carbonate, magnesium and sodium is lower in the surface layer and increases in layer closer to the dentinoenamel junction (DEJ). The surface layer is lower in carbon dioxide, which allows to dissolves at a slower rate in acids and contains less organic and water content.
- The age changes in enamel such as decrease in density and permeability, and an increase in nitrogen and fluoride content causes teeth to become more resistant to dental caries with time.

Morphologic characteristics

- Presence of deep, narrow occlusal fissures or buccal and lingual pits predisposes to development of caries as they tend to trap food, bacteria (cariogenic) and debris and also protect them from the attack of host immune system.
- As age advances, attrition of inclined planes becomes flattened, provides

less opportunity for entrapment of food in the fissures, as a result there is less occlusal caries in senile patient.

Position

- The tooth which is malaligned in the arch, rotated or out of position is more predisposed to caries in a susceptible individual as it tends to accumulate more of food debris, cariogenic plaque and bacteria.
- Also, such teeth are inaccessible for cleaning.

Saliva

The teeth are constantly bathed in saliva and to certain extent saliva definitely has its effect in both predisposition and prevention of dental caries. The nature of saliva is complex owing to its great variation in its composition making it difficult to ascertain the direct influence of the factors that influence development of dental caries.

Composition

1. Inorganic components of saliva

- They include calcium and phosphate concentration in saliva, other components like sodium, chloride and fluoride.
- Under normal conditions, saliva is supersaturated with calcium and phosphate ions. This prevents enamel from dissolving and tends to precipitate apatite crystals in the surface enamel of carious lesion thus helping in partial repair of tooth damaged by caries and this process is also referred to as *remineralization*.
- During caries process, i.e. under low pH conditions, the saliva is unsaturated with calcium and phosphate ions leading to dissolution of enamel.
- Fluoride in saliva has profound effect in reducing the caries activity by following ways:
 - During development of tooth, systemically administered fluorides convert hydroxyl apatite crystals into fluoroapatite crystals which are highly resistant to acid attack.
 - It helps in remineralization of incipient caries by precipitating the lost mineral ions from the tooth surface.
 - It inhibits enzyme *enolase*, which is essential for carbohydrate metabolism and prevents degradation of carbohydrates and thus acid

formation and dissolution of enamel.
- It prevents the activity of *glucosyltransferase*, which prevents the formation of extracellular polysaccharides and reduces bacterial adhesion on to the tooth surface.
- It limits the rate of carbohydrate metabolism by the cariogenic bacteria and reduces the acid attacks on the tooth.
- Fluoride ions can be directly toxic to *Streptococcus mutans* under high concentrations.

2. Organic components of saliva

- It includes mucin, ammonia, urea, thiocyanate, secreted carbohydrates and enzymes like amylase and urease.
- It is suggested that high concentrations of ammonia to some extent retard plaque formation and neutralize acid.
- Urea may be hydrolysed to ammonium carbonate by urease and increase the neutralizing power of saliva.
- Salivary amylase helps in degradation of starch and makes them more soluble so that it is easily washed away from the tooth surface.

pH

- Even though pH of saliva shows great variation, it falls in a narrow range for most individuals.
- *Critical pH*: It is the pH at which saliva ceases to be saturated with calcium and phosphate ions. Below this value, the inorganic content of tooth starts dissolving. The critical pH is about *5.5*. As the hydrogen ion concentration in a cariogenic plaque increases, more of phosphate ions leave the tooth surface.
- The buffering capacity of saliva is another factor which plays an important role in carious process. The chief buffering system includes: bicarbonate–carbonic acid and phosphate system. The bicarbonate ions diffuse into dental plaque and neutralize the acid formed during caries process.
- Higher the flow rate, greater will be the buffering capacity.

Quantity

- Dental caries activity is inversely proportional to quantity of saliva.
- More the amount of salivary flow, less is the caries index, as it increases clearance of bacteria and food debris from the tooth surface.
- This is more evident in case of salivary gland aplasia and xerostomia

conditions, where there is almost complete lack of saliva leading to rampant caries.
- Hyposalivation is a consequence of pathological conditions like diabetes, uraemia, etc. or due to usage of antisialogogues like atropine, etc.

Viscosity

High caries incidence is associated with thick mucinous saliva as it fails to produce adequate cleaning action.

Antibacterial factors

- Saliva contains many antibacterial factors like lysosome, salivary peroxidase system and immunoglobulins.
- Lysosome in the presence of sodium lauryl sulphate can lyse many cariogenic and noncariogenic streptococci. Lysosomal activity is seen more in caries-free group than caries-prone group.
- Salivary peroxidase and thiocyanate system inactivates many bacterial enzymes of glycolytic pathway and inhibit their growth. This system is more effective against *Lactobacillus acidophilus* and *S. cremoris*.
- Secretory immunoglobulin IgA is the most predominant immunoglobulin seen in saliva that inhibits cariogenic bacteria, especially the *S. mutans*.

Diet

Physical factors

- The form of food is an important factor responsible for the differences in caries experience between primitive and modern man.
- Raw unrefined foods contain great deal of roughage which cleanses the teeth. Also, presence of soil and sand induces attrition of both occlusal and proximal surfaces of the teeth and reduces dental caries.
- Soft and refined foods tend to stick to the teeth increasing accumulation of debris.

Local factors

- **Carbohydrate:** This is the most important factor in dental caries process. The principle carbohydrates in human diet are starches, sucrose, lactose, glucose, fructose or maltose. The synthesis of extracellular polysaccharide, glucans and levan, helps in adherence of bacteria to teeth. Starches are prevented from direct entry into plaque because of limited

diffusion of such large molecules.

- **Lipids:** Medium chain fatty acids and their salts have antibacterial properties at low pH.
- **Vitamin**
 - Vitamin A has definite effect on developing teeth, but it has no direct significant relation to dental caries.
 - Vitamin D is also necessary for the development of teeth.
 - Deficiency of these vitamins leads to enamel hypoplasia, which leads affected teeth susceptible to caries.

Systemic conditions

- **Heredity:** There may be some relation to dental caries. The possibility exists through inheritance of tooth form or structure that predispose to caries.
- **Pregnancy and lactation:** There may be increased caries incidence, especially during later stages of pregnancy due to lack of routine oral hygiene practice.

Classification and types of dental caries

Classification of Dental Caries (Table 8.3)

- Based on location
 - Pit and fissure
 - Smooth surface caries
 - Root caries
- **Based on structure of tooth involved**
 - Enamel
 - Dentine
 - Cementum
- **Based on onset and progression of dental caries**
 - Acute
 - Chronic
 - Incipient
- **Based on chronology**
 - Infancy (nursing bottle syndrome)
 - Adolescent
 - Adult
- **Based on site of tooth involved:** Class I, II, III, IV, V, VI *(according to Black)*

- Based on whether it is new or occurring at margin of restoration
 - Primary
 - Recurrent (secondary)
- **Based on senility of dental caries**
 - Rampant
 - Arrested
- **Miscellaneous:** Radiation caries

Table 8.3

Classification of dental caries

Type of caries	Location	Features	Progression
Pit and fissure caries	• Developmental pits and fissures with high steep walls and narrow bases result in poor self-cleansing action • Occlusal surfaces of molars and premolars • Buccal surfaces of molars • Lingual surfaces of molars • Lingual surfaces of maxillary incisors	• Brown or black • Little softening and opaqueness of surface • Feeling of *catch point* may be felt with tip of explorer • Bluish-white opacity of enamel directly bordering the lesion (due to undermining)	• *Initial stage*: Smaller in size • *Advanced stages*: Wider, which spread towards dentine, due to typical orientation of enamel rods • When they reach DEJ, they spread laterally, which undermine the enamel • There may be a large carious lesion with tiny opening due to undermining of enamel
Smooth surface caries	• Smooth surface of teeth • Proximal surfaces of all teeth, i.e. just below contact point • Gingival third of buccal surfaces and lingual surfaces of all teeth	• In early stages, well-demarcated, chalky-white opacity of enamel is seen under dry conditions • Well-demarcated, yellow or brown pigmented area of enamel is present • Roughened surface, due to demineralization of enamel is present • No loss of tooth surface continuity is seen • Bluish-white opacity of enamel directly borders the lesion	• Initially, a narrow spot is seen • Later, it may extend both buccally and lingually
Linear enamel caries Atypical form of dental caries observed in primary dentition of children	• Region of neonatal line • Labial surface of anterior maxillary teeth	Gross destruction of labial surfaces of incisor teeth	
Cervical caries Directly related to lack of oral hygiene	• Cervical region of teeth • Buccal surfaces • Lingual surfaces • Labial surfaces	To begin with crescent-shaped cavity, slightly roughened chalky area, later it becomes excavated	• Always an open cavity • No narrow point of penetration
Root caries (cementum caries)	Found in dentitions of older age group with gingival recession	Initiates on cementum on the root surface, initially chalky white in colour, later a cavitated lesion of dark brown colour results	Initially a narrow opening will be present, gradually surface layer of cementum lost and become cavitated
A soft progressive lesion that is always found anywhere on the root surface that has lost connective tissue attachment and is exposed to oral environment	• Buccal and lingual surfaces of roots • Teeth most frequently affected are first mandibular molar, mandibular premolars, and maxillary cuspid • Least affected: Mandibular incisors		
Rampant caries— Acute, fulminating type of carious process characterized by simultaneous involvement of multiple number of teeth in multiple surfaces of teeth	• Proximal surfaces and cervical surfaces of mandibular incisors • *Characteristics of rampant caries:* Increase in 10 or more new carries lesions over a period of one year • *Age of occurrence of lesion:* 4–8 years for deciduous teeth and 11–19 years for permanent teeth • It can occur in persons with no previous history of dental caries • It can occur in persons with good oral hygiene habits	• Rapid coronal destruction within short-span of time, causing early involvement of the pulp • Not possible for pulp to make secondary dentine	

Nursing bottle caries (Baby bottle syndrome)— It is an acute carious lesion	• Children taking milk or fruit juices by nursing bottle for longer duration of time preferably during sleep • Maxillary anterior teeth, I molars, cuspids are commonly involved • Mandibular anterior teeth are usually spared (as they are covered by tongue)	Spread within a short span of time, causing early involvement of the pulp	
Chronic caries— • Progression at a slower pace • Rarely causes pulp involvement • Pulp gets sufficient time to produce secondary or reactionary dentine to protect itself	Any teeth can be involved	• Shallow cavity with minimum softening of dentine • Little undermining is seen • Moderate lateral spread can be noticed	Entrance to lesion is almost larger than in acute caries
Arrested caries— • Progression ceased after initial development • It can occur both in enamel and in dentine	• Both deciduous and permanent dentitions are affected • More commonly seen on occlusal surface	• Characterized by large open cavity in which there is lack of food retention, superficially softened and decalcified dentine, which gradually get burnished and appears hard, black or brown-coloured dentinal surface at its base—*eburnated dentine* • Sclerosis and secondary dentine formation occurs	Large open cavity is invariably present
Recurrent caries	Begins around the margins or at the base of a pre-existing defective restoration		
Forward caries	Progression of carious lesion unidirectionally from enamel into dentine and pulp		
Backward caries	Progression of carious lesion bidirectionally from enamel into dentine and later from dentine into enamel at a different location		

Radiation caries

- This is seen in patients undergoing radiation therapy in head and neck region.
- Xerostomia, increase in viscosity and low pH of saliva are noted after irradiation, which predispose to caries.
- Three forms of dental defects are noted:
 1. Caries like lesion usually completely encircling the neck of the tooth leading amputation of crown sometimes. The lesion also extends to buccal, labial or lingual surfaces.
 2. This type of lesion begins as brown to black discolouration of the crown. The occlusal surface of posterior teeth and incisal edges of anterior teeth wear away.
 3. It begins as a spot depression, which spreads from incisal or occlusal edges on labial or buccal and lingual surfaces.

Histopathology of dental caries

- The study of morphological and biochemical events of dental caries is challenging because of technical problems involved in the preparation of hard tissue for examination.
- Ground sections (60–100 microns thickness) is usually used to study enamel caries and other hard tissues.

- Though dental caries is basically a demineralization process, the decalcification is necessary for cutting thin sections to study soft tissue histopathology but it results in complete loss of enamel unless special methods are used.

Methods used to study dental caries

- Ground sections
- Histopathological techniques
- Histochemistry and radioisotopes
- Microradiography
- Scanning electron microscopy (SEM) and transmission electron microscopy (TEM)

Enamel caries

- Depending upon site of involvement, enamel caries may be smooth surface caries or pit and fissure caries.
- Depending upon the degree of advancement, enamel caries may be early or advanced caries.

Smooth surface enamel caries

Early enamel caries

- The earliest macroscopic evidence of incipient caries is the appearance of an area of decalcification beneath the dental plaque which resembles a smooth chalky white area, especially at the cervical margin of the interdental facet—*white spot.*
- The intact surface lesions may also appear brownish in colour—*brown spot,* which depends on the degree of exogenous materials absorbed by the porous region.
- Loss of interprismatic or interrod substances with increased prominence of enamel rods.
- Appearance of transverse striations of enamel rods.
- Appearance of dark lines perpendicular to enamel rods.
- Accentuation of incremental striae of Retzius (optical phenomenon).

- Accentuation of perikymata.

Advanced enamel caries: Advanced enamel caries microscopically presents four distinguishing zones starting from the inner advancing front of the lesion, namely (Fig. 8.1):

- Zone 1: Translucent zone
- Zone 2: Dark zone
- Zone 3: Body of the lesion
- Zone 4: Surface zone
- **Zone 1: Translucent zone**
 - It is the first recognizable zone, which occupies half of the lesion.
 - It is seen only when a longitudinal ground section is examined in a clearing agent having a refractive index identical to that of enamel. Quinolone is more suitable since its refractive index is identical to that of the enamel (RI: 1.62).
 - When ground section is examined in transmitted light, after imbibition with quinoline, the transmitted zone appears structureless.
 - Location: Deepest zone or advancing front of advanced enamel caries.
 - Porosity: More and larger than normal enamel (0.1%).
 - Volume of spaces: 1%.
 - Demineralization is seen at the junction of prismatic and interprismatic enamel. Only the magnesium- and carbonate-rich minerals are affected. There will be no evidence of protein destruction.
- **Zone 2: Dark zone**
 - It is called so because of excessive demineralization and dark appearance in ground sections, when examined by transmitted light after imbibition with quinoline.
 - The pores are filled with air or vapour and when light scattered on passing through the zone, causes brown discolouration of this zone.
 - It is narrower in rapidly progressing caries and wider in slowly progressing caries.
 - It is a positive zone, because it is usually present.
 - Location: It is located just superficial to translucent zone.
 - Pore volume is 2–4%.
 - It is called *positive zone* as it produces positive birefringence in contrast to negative birefringence of sound enamel because of small pores compared to translucent zone.
- **Zone 3: Body of the lesion**
 - Location: It is seen between the dark zone and the surface layer of

enamel.
- Greatest demineralization is seen.
- Pore volume (polarized light): 5% at the periphery, 25% at the centre.
- Demineralization site includes both periphery and central areas of the rods.
- Accentuation of striae of Retzius.
- It consists more of water and organic content due to the ingress of bacteria and saliva.

- **Zone 4: Surface zone**
 - It remains comparatively unaffected despite subsurface demineralization and also to surface remineralization.
 - It is about 40 μm in thickness.
 - 1–10% loss of mineral salts is seen.
 - Pore volume: <5%.
 - Polarized light: Negative birefringence.
 - It is more mineralized because of more mineral (fluoride) content and insoluble proteins.
 - It will be intact and well mineralized because of calcium and phosphate ions released by subsurface dissolution, which may reprecipitated. This process is referred to as *remineralization*.

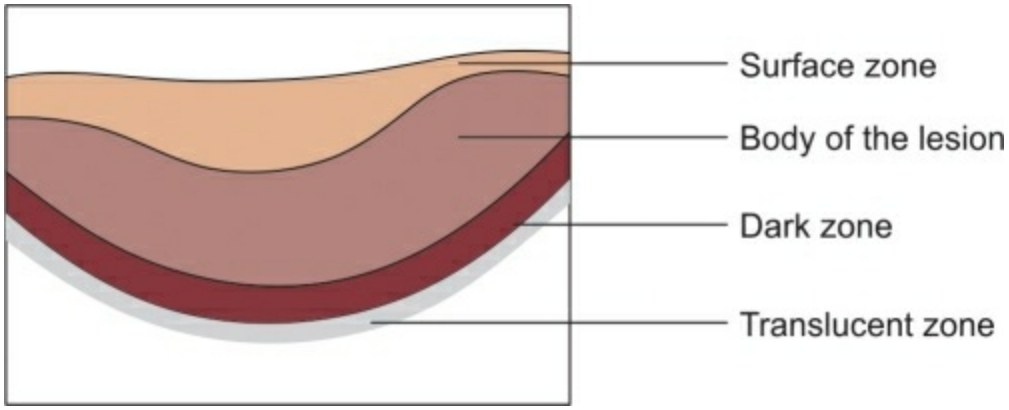


FIG. 8.1 Zones of advance enamel caries.

Pit and fissure enamel caries

- The carious process in pits and fissures is similar to that seen in smooth surface caries except as the variations in anatomical and histological structure dictate.

- The occlusal fissures are deep invaginations of enamel that have been described as broad or funnel-shaped, constricted hour glass, multiple invaginations with inverted Y-shape divisions or irregularly shaped.
- Pits and fissures often cause food stagnation with bacterial decomposition at the base.
- The carious lesion more often starts at both sides of the fissure wall rather than at the base and visual changes such as chalkiness or yellow, brown or black discolouration may be seen.
- The enamel at the bottom of the pit or fissure may be very thin, so that early dentine involvement frequently occurs. On the other hand, some pits and fissures are shallow and have a relatively thick layer of enamel covering their base.
- In both types, the enamel rods flare laterally in the bottom of the pits and fissures. The caries follows the direction of the enamel rods and characteristically forms a triangular or cone-shaped lesion with its apex at the outer surface and its base towards the dentinoenamel junction (opposite of that occurring on smooth surfaces). Because of this shape, greater number of dentinal tubules are involved when the lesion reaches the dentinoenamel junction.

Ultrastructural changes in enamel caries

- The first alteration found in enamel is the scattered destruction of individual apatite crystals, both within the enamel prisms and at their borders.
- Later, demineralization occurs both from the periphery and from the centre of the rods resulting in increased intercrystalline gap.
- Sometimes remineralization occurs and there will be change in the structure of crystals due to the combined effect of demineralization and remineralization.

Dentine caries (fig. 8.2)

- Dental caries in enamel is clearly a dynamic process, but tissue is incapable of reacting in a vital manner as it is devoid of cells.
- Dentine being a part of the dentine–pulp complex is able to mount a reparative response.
- Caries of the dentine begins with the natural spread of the process along the dentinoenamel junction and the rapid involvement of great numbers of dentinal tubules, each of which acts as a tract leading to the dental

pulp along which the microorganisms may travel at a variable rate of speed, depending upon a number of factors.

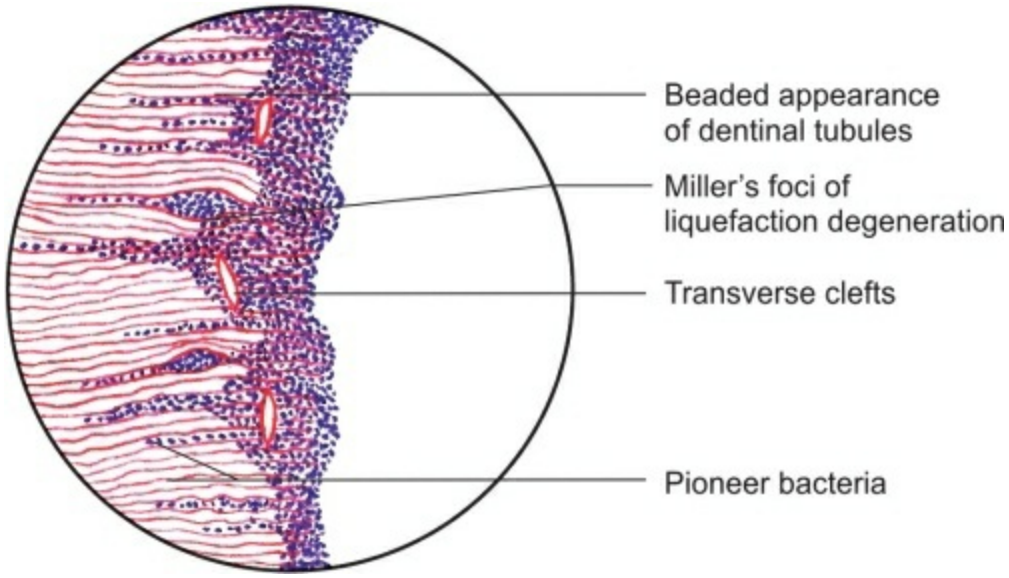


FIG. 8.2 Histopathology of dentine caries.

Early dentinal changes

- **Zone 1: Zone of fatty degeneration of Tomes' fibres**
 - Deposition of fat globules precedes early sclerotic changes.
 - Special stains like Sudan red reveals a superficial layer of bacterial origin and lipids present in intraglobular dentine.
 - Significance: Fat contributes to impermeability and it may be a predisposing factor for dental sclerosis.
- **Zone 2: Zone of dentinal sclerosis**
 - The initial penetration of the dentine by caries may result in alterations in the dentine, which is described as *dental sclerosis* or *transparent dentine formation*.
 - It is a reaction of vital pulp—calcification of dentinal tubules.
 - It seals off dentinal tubules from further penetration of microorganisms.
 - Sclerosis will be minimal in rapidly progressing dental caries, whereas it will be prominent during slow rate dental caries.
- **Zone 3: Zone of decalcification of dentinal tubules**
 - It will be present above dentinal sclerosis.

- It occurs in advance of bacterial invasion of dental tubules.
- In the earliest stages of caries, when only a few tubules are involved, microorganisms may be found penetrating these tubules before there is any clinical evidence of the carious process. These have been termed *pioneer bacteria*.
- The initial decalcification involves the walls of the tubules, allowing them to distend slightly as they become packed with masses of microorganisms.

- **Zone 4: Zone of microbial invasion**
 - Proteolytic organisms are predominant in deeper caries of the dentine. Acidogenic organisms are more prominent in early caries.
 - The observation that the morphologic type of the bacteria in deep carious dentine is different from that of the bacteria in initial caries substantiates the hypothesis that initiation and progression of dental caries are two distinct processes.

Advanced dentinal changes

- **Zone 5: Zone of decomposed dentine**
 - This is the outermost zone of the carious dentine and is characterized by complete destruction of dentinal tubules (as a result of their severe expansion due to accumulation of microorganisms and their by-products).
 - There is thickening of sheath of Neumann along its course.
 - The expanded tubules cause compression and bending of the adjacent tubules and eventually destroy them.
 - In this zone, the areas of decomposition of dentine, which occur along the direction of the dentinal tubules, are called *the liquefaction foci of Miller.*
 - In some areas, the cariogenic microorganism spreads laterally and large bacteria filled clefts develop at right angles to the direction of the tubules due to decomposition of dentine. These clefts are called *transverse clefts.* The mechanism of formation of transverse cleft is not clearly known; they may follow the course incremental lines or result from the coalescence of liquefaction of adjacent tubules. Transverse clefts may also arise by extensive proteolytic activity along the interconnecting lateral branches of the odontoblastic processes.
 - In this zone, bacteria may no longer remain confining within the dentinal tubules and they invade and destroy the peri- and intertubular

dentine. In this process, the entire dentinal structure is destroyed.

Diagnosis of dental caries

Diagnosis of dental caries is described in Table 8.4.

Table 8.4

Diagnosis of dental caries

Test	Procedure/characteristics	Significance
Clinical examination: Caries is detected by observing the changes in translucency of enamel in a clean, dry and well-illuminated field • Use of only visual examination method is known as *European method* • Use of sharp or blunt probe with visual examination *is known as American method*	*Black* suggested the use of a sharp explorer: • Use of mirror and sharp probe • Mirror and blunt probe • Tooth separation: To visualize posterior proximal surfaces Uses orthodontic modules or bands	• If slight pull is required, i.e. if there is any *catch*, then the surface is counted as being decayed • Most commonly used method • Blunt probe is used to remove plaque and debris from the fissures • Impression of the proximal surfaces can be taken to detect cavitation
Radiographic examination: Dental radiographs include: • Periapical • Panoramic • Bitewing	Extension of enamel radiolucency up to DEJ indicates cavitations on tooth and involvement of underlying dentine	• *Pit and fissure caries:* Triangle-shaped radiolucent area with base located towards the DEJ • *Smooth surface caries:* Triangle-shaped radiolucent area with base located towards the surface of the tooth • *Root caries:* U-shaped radiolucent area with irregular margins
Infrared laser fluorescence (ILF)	• It is used both for occlusal and smooth surface caries • It uses a laser light source and a fibreoptic cable that transmits the light to a hand-held probe with a fibreoptic eye at the tip. The absorbed light induces infrared fluorescence which is collected at the probe tip and transmitted through ascending fibres, processed and presented on a display window as an integer between 0 and 99	Increased fluorescence reflects carious teeth, particularly if its numerical value is more than 20
Digital imaging fibreoptic transillumination (DFT)	It provides an intense light beam transmitted through a fibreoptic cable to a specially designed probe to permit the use of transillumination on the proximal surfaces of posterior teeth	It provides visually observed images, which are captured using digital charge-coupled device camera and sent to a computer for analysis, using dedicated algorithm
Quantitative light fluorescence (QLF)	It is a dental diagnostic tool for in vivo and in vitro quantitative assessment of dental caries, dental plaque, bacterial activity, calculus, staining, tooth whitening	The contrast between sound and demineralized enamel increases almost by a factor of 10
	It is based on the auto-fluorescence of teeth; when tooth is illuminated with high-intensity blue light, they will start to emit light in the green part of the spectrum	Also the absence of specular reflections in the QLF images makes it much easier for the digital image processing system to calculate size and severity of lesion
Use of caries detector dyes	The altered enamel areas contain more reactive calcium that reacts with carboxylic and sulphonic dyes	Various dyes such as silver nitrate, methyl red and alizarin stain are used

Xeroradiography	Areas of subtle density differences are made more visible	• It demonstrates broader latitude of enhancement called *edge exposure* • The areas of subtle density differences are made more visible
Ultrasound	• Used on easily accessible areas but not for interproximal surfaces • Mainly used in the in vitro studies	Uses sonar device in which beam of ultrasound wave is directed against the tooth surface and reflected wave is picked up by an appropriate receiver
Optical caries monitor	To quantify smooth surface lesions	The dental caries lesions reflect much light than sound enamel
Endoscopic methods	This gives a magnified image of carious lesion	
Diagnodent	• Detect early stage of initial lesions • The incidence of fissure, proximal and residual caries can be identified	A laser diode provides light of a defined wavelength that is directed on to the tooth; when the incident light meets a change in tooth substances, it stimulates fluorescent light of a different wavelength; this is then evaluated by an appropriate electronic system in the control unit

Prevention of dental caries

Methods of dental caries control can be classified into three general types (Table 8.5):

1. Chemical measures
2. Nutritional measures
3. Mechanical measures

Table 8.5

Classification of methods of dental caries control

Chemical measures	Nutritional measures	Mechanical measures
• **Substrates which alter the tooth surface fluorine** • Water fluoridation • As supplements • Topical fluorides • In dentifrices • Mouth rinses **Bis-biguanides, chlorhexidine and alexidine:** These are most effective anticaries and plaque control agents *Disadvantages* • Bitter taste • Brownish discolouration of teeth and gingiva • Painful desquamation of mucosa **Silver nitrate:** It is believed that, it plugs both organic and inorganic pathways of enamel combining with the soluble inorganic portion of enamel to form a less soluble combination **Zinc chloride and potassium ferrocyanide:** It impregnates enamel and block pathway of caries but is of little clinical value	• **Restriction of refined carbohydrate intake** • Eliminate sucrose from the diet or reduce the amount • Eliminate the sucrose in between meals and snacks • **Phosphate-rich diet**	• **Dental prophylaxis:** Polishing of roughened tooth surface and correction of faulty restorations → reduces bacterial plaque formation → reduces development caries • **Tooth brushing** • Most widely accepted method • More effective, if used with fluoride dentifrices • Minimum of 5 minutes, daily along with other interproximal cleansing aids is recommended • **Mouth rinsing** • It loosens food debris that accumulate on the tooth surface → reduces plaque → reduces caries incidence • Dextranase agent → hydrolyse streptococcal polysaccharide → plaque reduction • **Dental floss:** To remove interproximal plaque and also promotes gingival health
• **Substances which interfere with carbohydrate degradation through enzymatic alterations** • Vitamin K • Sarcosine Both of them are thought to decrease acid production by interfering with carbohydrate degradation and thereby reduce caries experience • **Substances which interfere with bacterial growth and metabolism** • *Urea and ammonium compounds* • *Chlorophyll* • *Antibiotics:* – Penicillin – Erythromycin – Kanamycin – Spiramycin – Tetracycline – Tyrothricin – Vancomycin • **Plaque controlling agents** • Antiseptic agents: – Positively charged agents like quaternary ammonium compounds, pyrimidines, bis-biguanides – Non-charged agents like listerine, triclosan, phenol and thymol – Oxygenating agents like peroxides and perborates – Halogens – Heavy metal salts • *Antibiotics:* Neomycin, kanamycin, tetracycline, vancomycin • *Enzymes:* Mucinases, pancreatin, fungal enzymes and proteases • *Plaque-modifying agents:* Urea peroxide • *Sugar substitutes:* Xylitol, mannitol • *Plaque attachment interference agents:* Sodium polyvinyl, phosphoric acid and perfluoroalkyl		• **Oral irrigators** • It includes various irrigants to flush the mouth for therapeutic purposes • It promotes gingival health, but it has limited value in preventing dental health • **Detergent foods:** Fibrous foods → prevent lodging of food in pits and fissures (act as detergent) → reduce dental caries • **Chewing gum** • Prevents dental caries by mechanical cleansing action • Chew it for at least 10 minutes after morning and evening meals • *Xylitol* (sugar substitute) sweetened chewing gum → significantly reduce *S. mutans* level in both saliva and plaque, increase plaque pH by increasing salivary secretion and promotes remineralization • Chewing gums are also used as fluoride vehicle • **Pit fissure sealant** • It seals pit and fissures on the occlusal surface, thereby reducing the entry of bacteria into these areas and it reduces caries incidence • Few sealants also contain fluoride

Dental caries activity tests

- *Dental caries activity test* measures the degree to which the local environment challenge favours the probability of carious lesion.

 - It predicts caries activity or patient susceptibility to dental caries.
 - It acts as a valuable adjunctive for patient's motivation in caries prevention.
 - It establishes the need for personalized preventive measure.
 - It provides an index of success of therapeutic procedures.
 - It monitors effectiveness of education program.
- *Dental caries activity* refers to the increment of active lesions (new or recurrent) over a slated period of time.
- *Dental caries susceptibility* refers to the inherent tendency of host and the target tissue, the tooth to be afflicted by the caries process.
- Dental caries activity tests are described in Table 8.6.

Table 8.6

Dental caries activity tests

Test	Principle	Procedure	Interpretation
Lactobacillus (LB) colony test	This method, first proposed by *Hadley*, measures the number of colonies on the selective medium, which reflects the quantity of acidic flora in the patient's mouth	• Inoculation and incubation of patient's saliva in tomato peptone agar with pH 5.0 • Rogosa medium is highly selective	**No. of LB/ml saliva Caries activity** 0–1000 Little or None 1000–5000 Slight 5000–10000 Moderate >10000 Marked
Colorimetric Snyder test	• It is first proposed by *Snyder* • This test is based on rate of acid produced by acidogenic flora	• Simulated saliva is inoculated into glucose and agar containing medium with pH 4.7–5.0 • Colour indicator: Bromocresol green (changes from blue-yellow) is used • The acid produced by the oral acidogenic flora is detected by the changes in pH indicator and compared to an uninoculated control at 24, 48, 72 hrs of incubation	**Time 24 48 72** **(in hrs)** Colour Yellow Yellow Yellow Caries Marked Definite Limited activity Colours Green Green Green Caries Continue Continue Inactive activity test test
Swab test	The principle is same as Snyder's test	• Oral flora collected by swabbing buccal surfaces of teeth and incubated for 48 hrs • Colour indicator is used; pH is measured directly using pH meter • Colour changes are read using colour comparator	**pH Caries activity** <4.1–4.1 Marked 4.2–4.4 Active 4.5–4.6 Slightly active >4.6 Inactive
Salivary *S. mutans* level test	Number *S. mutans* formed per unit volume of saliva	Incubation of sample (plaque/saliva) on mitissalivarius agar (MSA) with 20% sucrose, 0.2 U bacitracin/ml, 95% N_2-5% CO_2 for 48 hrs at 37°C	Levels of *S. mutans* greater than 10^5/ml—caries prone individuals
S. *mutans* dip-slide method	Density of S. *mutans* colonies growing on modified MSA compared with model chart	Stimulated saliva is collected and poured over agar coated slide and excess is drained	*S. mutans* (CFU/ml) Score of saliva Negligible 0 <100,000 1 100,000–1,000,000 2 >1,000,000 3
		• Slides are dried and bacitracin discs are placed in the middle of inoculated agar about 1 cm apart from each other • The slide is then incubated in a tube containing CO_2 for 48 hrs • Zone of inhibition formed around each disc is measured • If present *S. mutans* appears as small blue colonies growing within the zone of inhibition • The colony density is compared with a model chart	

Key points

- *Dental caries* can be defined as a progressive, post-eruptive, microbial disease affecting dental hard tissues resulting in demineralization of the inorganic constituents and dissolution of the organic components, which often leads to cavitation.
- *Miller's chemoparasitic theory (Willoughby D Miller, 1882):* Dental decay is a chemicoparasitic process consisting of two stages: the decalcification of enamel which results in its total destruction and the decalcification of dentine as a preliminary stage, followed by dissolution the softened

residue. In case of enamel, however, the second stage is practically wanting, the decalcification of enamel signifying its total destruction.

- *Pit and fissure caries: S. mutans, S. sanguis, Lactobacillus* species, *Actinomyces* species.
- *Smooth surface caries: S. mutans, S. salivarius.*
- *Root surface caries: A. viscosus, A. naeslundii, S. mutans, S. sanguis*.
- *Deep dental caries: Lactobacillus* sp., *A. naeslundii*, other filamentous rods.
- *Proteolytic theory (Gottlieb, 1944):* Caries is essentially a proteolytic process —the microorganisms invade the organic pathways and destroy them in their advance, acid formation accompanies proteolysis.
- Proteolysis–chelation theory (Schatz, 1955): Simultaneous microbial degradation of the organic components and the dissolution of the minerals of the tooth by the process known as *chelation*.
- Zones of enamel caries: Translucent zone, dark zone, body of the lesion and surface zone.
- Zones of dentinal caries: Zone of fatty degeneration of Tomes' fibres, zone of dentinal sclerosis, zone of decalcification of dentinal tubules, zone of microbial invasion and zone of decomposed dentine.
- Diagnostic aids for dental caries: Clinical examination, radiographic examination, infrared laser fluorescence, digital imaging fibre optic transillumination, quantitative light fluorescence, caries detector dyes, xeroradiography, ultrasound, optical caries monitor, endoscopic methods and diagnodent.
- Dental caries activity tests: Lactobacillus (LB) colony test, Snyder test, Swab test, salivary *S. mutans* level test, *S. mutans* dip-slide method, buffer capacity test, salivary reductase test and enamel solubility test.

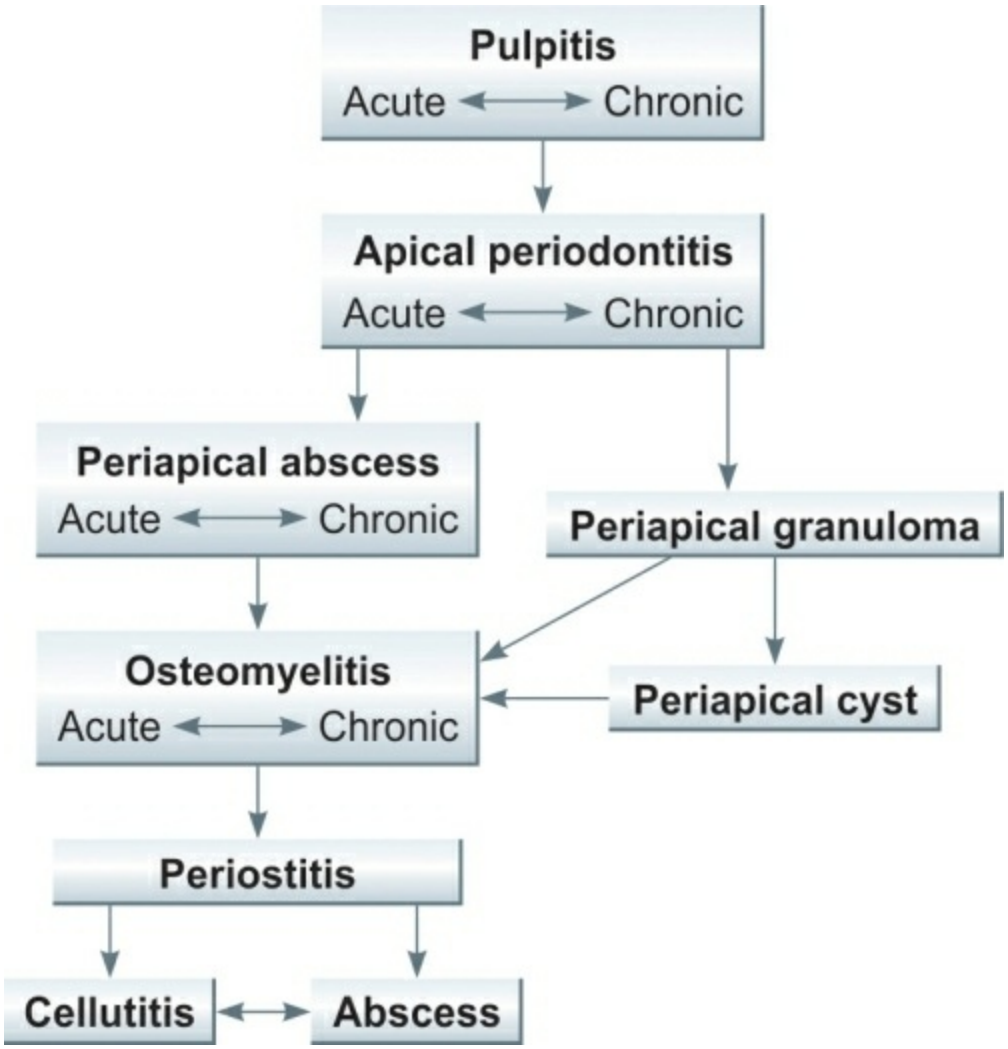
Frequently asked questions

1. Classify dental caries and write about chemoparasitic theory of dental caries.
2. Theories of dental caries.
3. Aetiology of dental caries.
4. Pit and fissure dental caries and smooth surface dental caries.
5. Histopathology of dental caries.
6. Diagnosis of dental caries.
7. Discuss the chemical measures to control dental caries.
8. Dental caries activity tests/Snyder's test.

CHAPTER 9

Diseases of dental pulp and periapical tissues

Sequelae of diseases of dental pulp and periapical tissues are given in Flowchart 9.1.



FLOWCHART 9.1 Sequelae of diseases of dental pulp and periapical tissues

Microbiology of disease of dental pulp and periapical tissues

Microorganisms virtually cause all the pathoses of the pulpal and periapical tissues. The root canal infection develops after pulpal necrosis, which can occur usually as a sequel of caries, trauma, periodontal diseases or operative procedures.

Bacterial pathways into the pulp

Bacteria enter the pulp in following ways:

- Through dentinal tubules following carious invasion
- Through crown or root following traumatic exposure of the pulp
- Coronal leakage following restorative procedures and restorations
- Through external or internal resorption that can lead to pulp exposures
- From the periodontal tissue through exposed dentinal tubules, lateral and accessory canals or apical and lateral foramina
- By the lymphatic or haematogenous route (*anachoresis*, defined as the localization of transient bacteria in the blood into an inflamed area, such as traumatized or inflamed pulp)

Bacterial genera prevalent in endodontic infections

Table 9.1 describes the bacterial genera which are prevalent in endodontic infections.

Table 9.1

Bacterial genera prevalent in endodontic infections

Anaerobic gram-negative bacteria	• *Treponema* • *Porphyromonas* • *Fusobacterium* • *Prevotella* • *Veillonella*
Facultative gram-negative bacteria	• *Neisseria* • *Capnocytophaga* • *Haemophilus*
Anaerobic gram-positive bacteria	• *Actinomyces* • *Propionibacterium* • *Peptostreptococcus* • *Filifactor*
Facultative gram-positive bacteria	• *Enterococcus* • *Actinomyces* • *Streptococcus* • *Lactobacillus*

Diseases of dental pulp

- The dental pulp is a delicate connective tissue that occupies the central portion of the tooth.
- It includes cellular constituents like odontoblasts, fibroblasts, undifferentiated mesenchymal cells and few inflammatory cells. The extracellular component consists of collagen fibres and ground substance. The dental pulp *mainly* consists of type I and type III collagen fibres. The ground substance includes glycosaminoglycans, hyaluronic acid, chondroitin sulphate, glycoproteins and water. The ground substance supports the pulpal cells and acts as a medium for transportation of nutrients and metabolites. The dental pulp is supplied by both afferent and efferent blood vessels through apical foramen and accessory canals. The nerve supply to the dental pulp is mainly by sensory fibres of trigeminal nerve and sympathetic branches from the superior cervical ganglion.
- The dental pulp responds to any noxious stimuli only through pain because it contains only pain receptors.
- The lack of collateral circulation in the dental pulp limits its capacity for healing.

Aetiology for diseases of dental pulp

The aetiology for dental pulp diseases is as follows (Grossman, 2010):

- **Physical**
 - ***Mechanical***
 - Trauma
 - – Accidental
 - – Iatrogenic dental procedures (during cavity or crown preparation)
 - Pathologic wear (attrition, abrasion, etc.)
 - Crack through body of tooth (cracked tooth syndrome)
 - Barometric changes (barodontalgia)
 - ***Thermal***
 - Heat from cavity preparation, at either low or high speed
 - Exothermic heat from the setting of cement
 - Conduction of heat and cold through deep fillings without a protective base
 - Frictional heat caused by polishing a restoration

- ***Electrical*** (galvanic current from dissimilar metallic fillings)
- **Chemical**
 - Phosphoric acid, acrylic monomer, etc.
 - Erosion
- **Bacterial**
 - Toxins associated with caries
 - Direct invasion of pulp from caries or trauma
 - Microbial colonization in the pulp by blood-borne microorganisms (anachoresis)

Note *Barodontalgia (aerodontalgia):* It denotes tooth pain occurring at low atmospheric pressure experienced either during flight or during a test run in a decompression chamber. Barodontalgia has generally been observed in altitudes over 5000 feet, but it is more likely to occur at 10,000 feet or above. A tooth with chronic pulpitis can be asymptomatic at ground level, but it may cause pain at high altitude because of reduced pressure.

Classification of dental pulp diseases

Diseases of dental pulp have been classified as follows (Grossman, 2010):

- **Inflammatory diseases of the dental pulp**
 - *Reversible pulpitis*
 - Symptomatic (acute)
 - Asymptomatic (chronic)
 - *Irreversible pulpitis*
 - Acute
 - – Abnormally responsive to cold
 - – Abnormally responsive to heat
 - Chronic
 - – Asymptomatic with pulp exposure
 - – Hyperplastic pulpitis
 - – Internal resorption
- **Pulp degeneration**
 - Calcific (radiographic diagnosis)
 - Others (histopathologic diagnosis)
- **Necrosis**

Reversible pulpitis

Definition

- It is a mild-to-moderate inflammatory condition of the pulp caused by noxious stimuli in which the pulp is capable of returning to the uninflamed state following removal of the stimuli.
- It is one of the earliest forms of pulpitis and is also referred as *pulp hyperaemia*.

Causes

Reversible pulpitis may be caused by any agent that is capable of injuring the pulp. The causes may be any of the following:

- Trauma, as from a blow or a disturbed occlusal relationship.
- Thermal shock, as from preparing a cavity with a dull bur or keeping the bur in contact with the tooth for too long or from overheating during polishing of a filling.
- Excessive dehydration of a cavity.
- Galvanism.
- Chemical stimulus, as from sweet or sour foods or from irritation of a silicate or self-curing acrylic filling.
- Cariogenic bacteria.
- Circulatory disturbances during pregnancy may also result in transient periodic hyperaemia.
- Local vascular congestion—usually associated with common cold or with sinus disease can cause a generalized transient hyperaemia of the maxillary posterior teeth.

Symptoms

- Symptomatic reversible pulpitis is characterized by sharp pain lasting for a moment.
- It is more often brought on by cold than hot food or beverages and cold air.
- It does not occur spontaneously and does not continue when the cause has been removed.
- Asymptomatic reversible pulpitis may result from incipient caries and is resolved on removal of the dental caries and proper restoration of the tooth.

Diagnosis

- Diagnosis is mainly by the study of the patient's symptoms and clinical tests.
- The pain is sharp, lasts for a few seconds and generally disappears when the stimulus is removed.
- Thermal changes particularly cold, sweet or sour usually cause the pain.
- Tooth with reversible pulpitis reacts normally to percussion and the periapical tissue appears normal on radiographic examination.

Histopathology

- Reversible pulpitis may range from hyperaemia to mild-to-moderate inflammatory changes limited to the area of the involved dentinal tubules.
- Reparative dentine, disruption of the odontoblastic layer, dilated blood vessels and extravasation of oedema fluid is seen.

Treatment

- Periodic care to prevent the development of caries, early insertion of a filling, if a cavity has developed, use of a cavity varnish or a cement base before insertion of a filling and care in cavity preparation and polishing are recommended to prevent pulpitis.
- Prevention is the best treatment for reversible pulpitis.
- Removal of the noxious stimuli usually suffices.

Prognosis

The prognosis for the pulp is favourable, if the irritant is removed early enough. Otherwise, the condition may develop into irreversible pulpitis.

Irreversible pulpitis

Definition

- Irreversible pulpitis is a persistent inflammatory condition of the pulp, symptomatic or asymptomatic, caused by a noxious stimulus.
- Acute irreversible pulpitis exhibits pain usually caused by hot or cold stimulus, or pain that occurs spontaneously. The pain persists for several minutes to hours, lingering after removal of the thermal stimulus.

Causes

The most common cause of irreversible pulpitis is bacterial involvement of the pulp through dental caries although any clinical, chemical, thermal or mechanical factors already mentioned as a cause of pulpal disease may also cause pulpitis. As previously stated, reversible pulpitis may deteriorate into irreversible pulpitis.

Symptoms

- In the early stages, a paroxysm of pain may be caused by sudden temperature changes particularly cold, sweet or acid food stuffs, pressure from packing food into a cavity and on lying down, which results due to congestion of blood vessels in the pulp.
- The pain often continues even after the removal of stimulus.
- The patient may describe the pain as severe, continuous, sharp, piercing or shooting-type.
- Pain may be intermittent or continuous in nature depending on the degree of pulpal involvement and on whether it is related to an external or internal stimulus.
- A change in position, that is on bending or lying down exacerbates the pain because of changes in intrapulpal pressure.
- The patient may have pain referred to the adjacent teeth and structures. The upper posterior tooth involvement produces pain in temple or sinuses, whereas lower posterior tooth involvement produces pain in the ear.

Diagnosis

- Clinical examination discloses a deep dental caries extending to the pulp or decay under a restoration.
- Probing of cavity elicits severe pain.
- Radiographic examination may not be significant.
- In the early stages of irreversible pulpitis, the thermal test may elicit pain that persists even after the removal of thermal stimulus, whereas in the later stages, pulp reacts feebly to heat and cold stimulations.
- The electric pulp test induces a response with marked variation in current from the normal.

Histopathology

- It shows both acute and chronic inflammatory changes.
- There will be increased vasodilatation accompanied by the accumulation of oedema fluid in the pulp.
- Large number of polymorphonuclear (PMN) leukocyte collections may be found beneath the area of carious penetration.
- Usually, localized destruction of the pulp by PMN leukocytes and formation of microabscess known as *pulp abscess* (acute suppurative pulpitis) is seen. Pulp abscess consists of pus arising from the breakdown of tissue, leukocytes and bacteria, which is surrounded by dense band of neutrophils and microorganisms. No microorganisms are found in the centre of the abscess because of the phagocytic activity of the PMN leukocytes.
- Sometimes, necrosis may be accompanied by tissue dehydration—*dry gangrene of pulp.*
- If the carious process continues to advance and penetrate the pulp, the histologic picture changes. The area of ulceration (chronic ulcerative pulpitis) is seen, that drains through the cavity and reduces the intrapulpal pressure and thereby the pain.
- Changes in odontoblastic layer may vary from disruption to total destruction.

Treatment

- It includes complete removal of the pulp (pulpectomy) and the placement of an intracanal medicament which act as a disinfectant or obtundent such as cresatin, eugenol or formocresol.
- Extraction of involved tooth should be considered, if the tooth is unrestorable.

Prognosis

The prognosis of the tooth is favourable, if the tooth undergoes proper endodontic therapy and restoration.

Chronic hyperplastic pulpitis

(Synonym: Pulp polyp)

Definition

Chronic hyperplastic pulpitis or pulp polyp is a productive pulpal inflammation due to an extensive carious exposure of a young pulp. This disorder is characterized by the development of granulation tissue, covered at times with epithelium and results from long-standing, low-grade irritation.

Causes

- Usually slow, progressive carious exposure of the pulp.
- For the development of pulp polyp, a large open cavity, a young resistant pulp and a chronic low-grade stimulus are necessary.
- Mechanical irritation from chewing and bacterial infection often provides the stimulus.

Symptoms

It is an asymptomatic lesion, except during mastication—the pressure from the food bolus may cause discomfort.

Diagnosis

- Generally seen among teeth of children and young adults.
- The appearance of polyp tissue is clinically characteristic as a fleshy, reddish, pulpal mass which fills most of the pulp chamber or cavity or extends beyond the confines of the tooth.
- Radiographs show a large open cavity with direct access to the pulp chamber.
- The tooth may respond feebly or not at all to the thermal tests unless extreme cold such as ethyl chloride spray is used.
- More current than normal may be required to elicit a response by means of electric pulp testing.

The appearance of hyperplastic pulpitis is characteristic and can be easily recognized, but it must be distinguished from the adjacent proliferating gingival tissue through probing and exploration.

Histopathology (fig. 9.1)

- Pulp polyp is a granulation tissue made up of delicate connective tissue fibres interspersed with variable numbers of small capillaries.
- Inflammatory cell infiltration consists of lymphocytes, macrophages, plasma cells and few PMN leukocytes.
- In some instances, fibroblasts and endothelial cell proliferations are

prominent.

- Surface of the polyp is usually covered by stratified squamous epithelium. (It may arise from desquamated epithelial cells from buccal mucosa or salivary gland ducts carried via saliva and transplanted to the surface of the pulp polyp.) Sometimes, rete peg formation is also seen.
- In time, organization of the tissue leads to decreased vascularity and increased fibrosis.

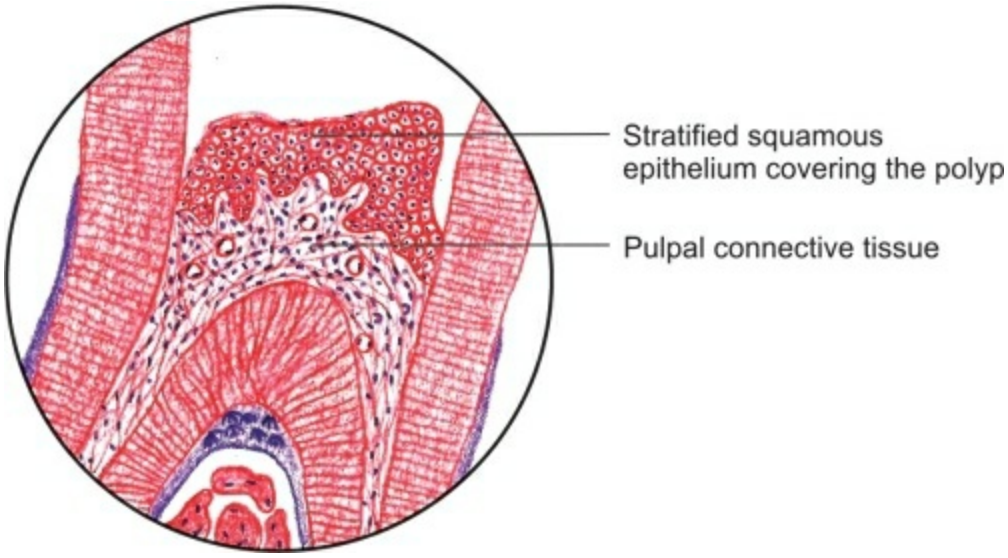


FIG. 9.1 Chronic hyperplastic pulpitis (pulp polyp).

Treatment

- Efforts at treatment should be directed towards elimination of the polyp tissue followed by extirpation of the pulp, provided the tooth can be restored.
- When the hyperplastic pulpal mass has been removed with a periodontal curette or spoon excavator, the bleeding can be controlled with pressure.
- The pulp tissue of the chamber is then completely removed and a dressing of formocresol is sealed in contact with the radicular pulp tissues. The radicular pulp is extirpated at a later visit. If time permits, the entire procedure of pulpectomy can be completed in a single visit.

Prognosis

The prognosis of the pulp is unfavourable but the prognosis of the tooth is

favourable after endodontic treatment and adequate restoration.

Internal resorption

It is discussed in Chapter 12 Regressive Alterations of the Teeth.

Pulp degeneration

- Degeneration of pulp may be due to persistent mild irritation in the teeth of younger people.
- It may not necessarily be related to infection or caries, although a cavity or a filling may be present in the affected tooth.
- The early stages of pulp degeneration usually do not cause definite clinical symptoms and the pulp may react normally to electric and thermal tests.
- As the degeneration progresses, the tooth may discolour and the pulp may not respond to stimulation.
- The specific types of pulp degeneration are:
 - Calcific degeneration
 - Atrophic degeneration
 - Fibrous degeneration

Calcific degeneration

It is discussed in Chapter 12 Regressive Alterations of the Teeth.

Atrophic degeneration

- This type of degeneration is usually seen in pulps of older individuals.
- Histopathologically, it shows fewer stellate cells and abundant intercellular fluid.
- The pulp tissue is less sensitive than normal.
- No clinical diagnosis exists.

Note: *Reticular atrophy* is an artifact produced by delay of the fixative agent in reaching the pulp and should not be confused with atrophic degeneration.

Fibrous degeneration

- This form of degeneration of the pulp is characterized by replacement of the cellular elements by fibrous connective tissue.
- On removal from the root canal, pulp has the characteristic appearance of a leathery fibre. This disorder causes no distinguishing symptoms to aid in clinical diagnosis.

Necrosis of dental pulp

Definition

- Necrosis of dental pulp is the death of dental pulp.
- It may be partial or total, depending on whether part of or the entire pulp is involved. Necrosis is normally the sequel to inflammation but it can also occur following a traumatic injury in which the pulp is destroyed before an inflammatory reaction can take place. As a result, an ischaemic infarction can develop and may cause a dry gangrenous necrotic pulp.
- Necrosis is of two types: (i) coagulation and (ii) liquefaction.
 - In coagulation necrosis, the soluble portion of tissue is precipitated or is converted into a solid mass. Caseation is a form of coagulation necrosis in which the tissue is converted into a cheesy mass consisting mainly of coagulation proteins, fats and water.
 - Liquefaction necrosis occurs when the proteolytic enzymes convert the tissue into softened mass, liquid or amorphous debris.

Cause

Necrosis of the pulp can be caused by any noxious insult injurious to the dental pulp such as bacteria, trauma and chemical irritation.

Symptoms

- Necrotic pulp causes no painful symptoms.
- Discolouration of the tooth is the first indication of pulp death.
- The tooth lacks its usual brilliance, luster and translucency.
- Teeth with partial necrosis can respond to thermal changes, owing to the presence of vital nerve fibres passing through the adjacent inflamed tissue.

Diagnosis

- Pain will be absent in a tooth with total necrosis.
- Swelling, mobility and response to percussion and palpation are negative.
- There will be no response to vitality tests also.

Histopathology

- Necrotic pulp tissue, cellular debris and microorganisms may be seen in the pulp cavity.
- The periapical tissue may be normal or slight evidence of inflammation of the apical periodontal ligament may be seen.

Treatment

Proper treatment of necrosis is the thorough canal debridement and obturation of the root canals.

Prognosis

The prognosis of the tooth is favourable, if proper endodontic therapy is instituted.

Diseases of periapical tissues

Pulpal diseases are one of the several possible causes of diseases of the periapical (periradicular) tissues. Because of the interrelationship between the pulp and the periradicular tissues, pulpal inflammation causes inflammatory changes in the periodontal ligament even before the pulp becomes totally necrotic. Bacteria and their toxins, immunologic agents, tissue debris, and products of tissue necrosis from the pulp reach the periradicular area through the various foramina of the root canals and causes inflammatory and immunologic reactions. Few neoplastic disorders, periodontal conditions, developmental factors and trauma can also cause periradicular diseases.

Classification of diseases of periapical tissues

Diseases of periapical tissues can be classified as follows (Grossman, 2010):

- **Acute periradicular diseases**
 - Acute apical periodontitis (symptomatic periodontitis)
 - Acute alveolar abscess
 - Acute exacerbation of chronic lesion (phoenix abscess)
- **Chronic periradicular diseases**
 - Chronic apical periodontitis
 - Chronic alveolar abscess
 - Cystic apical periodontitis/radicular cyst
 - Persistent apical periodontitis
- **Condensing osteitis**
- **External root resorption**
- **Diseases of the periradicular tissues of nonendodontic origin**

Acute apical periodontitis

(Synonym: Symptomatic apical periodontitis)

Definition

Acute apical periodontitis is a painful inflammation of the periodontium as a result of trauma, irritation or infection through the root canal regardless of the vitality of pulp.

Causes

- **In a vital tooth:** Occlusal trauma due to abnormal occlusal contacts, by a recently inserted restoration extending beyond the occlusal plane, by wedging of a foreign object between the teeth such as tooth pick, food, etc. or by blow to the teeth.
- **In a nonvital tooth**
 - As a sequelae of pulpal diseases, i.e. diffusion of bacteria or noxious products from an inflamed pulp.
 - Iatrogenic
 - Forcing of bacteria, debris, irritating irritants or medicaments through the apical foramen during root canal instrumentation.
 - Extension of the obturating material through apical foramen to impinge on periapical tissue.
 - Overinstrumentation during cleaning and shaping of the root canals.

Symptoms

- The tooth may be slightly painful, sometimes pain may be present only in a certain direction of percussion, or the soreness may be severe.
- The tooth may feel extruded and the patient may have pain on closure and mastication.

Diagnosis

- Pain on percussion is the classical diagnostic feature of apical periodontitis.
- Swelling is usually absent but a firm pressure on the mucosa over the root may create a positive response.
- Usually, there will be no response to electric and thermal pulp tests. But in the early stages, a positive response may be elicited due to residual fibres that are resistant to hypoxia and necrotic tissue, which can occur usually in multirooted teeth.
- Radiographic features may vary from normal to thickening of periodontal ligament space.

Histopathology

- Acute apical periodontitis is the initial exudative response at the periapical region.
- Pulpal hyperaemia—dilatation of the blood vessels is commonly seen.

- PMN leukocytes are predominantly present.
- Accumulation of the serous exudates distends the periodontal ligament and extrudes the tooth slightly.
- If irritation is severe, osteoclasts become active and may destruct the periapical bone.

Differential diagnosis

Acute alveolar abscess: It represents a further stage of development of disease with breakdown of periradicular tissue, rather than merely an inflammatory reaction of the periodontal ligament. The patient's history, symptoms and clinical test results help the clinician to differentiate these diseases.

Treatment

- Adjustment of high points (in hyperocclusion cases) and removal of irritants (in case of nonvital infected pulp) is the immediate line of management.
- When the acute phase has subsided, the tooth is treated endodontically.

Prognosis

- Usually favourable.
- Occurrence of the symptoms during endodontic treatment does not affect the outcome of the treatment.

Acute periapical abscess

(Synonyms: Acute alveolar abscess; acute abscess; acute dentoalveolar abscess; acute apical abscess; acute radicular abscess)

Definition

Acute periapical abscess is a localized collection of pus in the alveolar bone at the root apex of a tooth following death of the pulp with extension of the infection through apical foramen into the periradicular tissues.

Causes

- Dental caries, trauma, chemical or mechanical irritation.
- Because the pulp tissue is solidly enclosed, no drainage is possible and the

infection continues to extend in the direction of least resistance, i.e. through the apical foramen, and thereby involves the periodontal ligament and the periradicular bone.

Symptoms

- Usually, patients have severe throbbing pain and swelling of overlying soft tissues. As the infection progresses, swelling become more pronounced and extend beyond the original site and tooth becomes more painful and mobile. If left untreated, the infection may progress to chronic apical abscess wherein the contained pus may break through to form a sinus tract.
- Usually, swelling is seen in the adjacent tissues of affected tooth.
- The surface of the swelling appears taut and inflamed due to pus beneath it. Such liquefaction is the result of activity of proteolytic enzymes such as trypsin and cathepsin. The surface tissues become distended from the pressure of the underlying pus and finally rupture from this pressure and lack of resistance caused by continued liquefaction. The pus may extrude through a tiny opening, which becomes larger with time, or from two or more openings, depending on the degree of softening of the tissues and amount of pressure in the pus. The sinus tract ultimately heals by granulation after the elimination of the infection in the root canal.
- Systemic reactions: Patient may appear pale, irritable, weakened from pain, loss of sleep and slight rise in temperature. Fever is preceded by chills, headache and malaise.

Diagnosis

- Clinical examination and history.
- Intense and throbbing type of pain is present, which is localized to the involved tooth.
- Tenderness on percussion is present.
- Apical mucosa elicits tenderness on palpation.
- As the abscess extends towards the surface, swelling increases in size. Resorption of overlying bone and localization of suppuration produces a palpable fluctuant swelling.
- Radiograph shows dental caries below the defective restoration, thickened periodontal space or evidence of breakdown of bone at the root apex. Since the lesion is present for a shorter period of time, bone changes cannot be well appreciated in radiographs.

- The affected tooth will not respond to electrical or thermal tests.

Histopathology

- Marked infiltration of PMN leukocytes and the rapid accumulation of inflammatory exudates in response to an active infection distend the periodontal ligament and thereby elongate the tooth. If the process continues, the periodontal fibres get separated and the tooth becomes mobile.
- Although some mononuclear cells may be present, the chief inflammatory cells are PMN leukocytes. As the bony tissue in root apex is resorbed, more and more of PMN leukocytes die in their battle with microorganisms and pus is formed. Microscopically, empty space or spaces, where suppuration has occurred, surrounded by PMN leukocytes and mononuclear cells are seen.

Differential diagnosis

- Periodontal abscess: It is the accumulation of pus along the root surface of a tooth that originates from infection of supporting structures of the tooth. It is associated with pocket and is manifested by swelling and mild pain on pressure. Pus may extrude from the sulcus. Periodontal abscess is usually associated with vital tooth.
- Irreversible pulpitis.

Treatment

- Abscess drainage should be established through the root canal or by incision.
- Occlusion is relieved and a regimen of systemic antibiotics is prescribed. Pain often can be controlled with mild analgesics.
- Endodontic therapy is done only after the acute symptoms have subsided and while the patient is still receiving antibiotics.

Prognosis

- It is generally favourable depending on the degree of local involvement and amount of tissue destruction.
- When purulent material has been discharged from sulcus and periodontium is extensively destroyed, a combined periodontal and endodontic treatment will restore the tooth to functional health.

Chronic apical periodontitis

(Synonyms: Periapical granuloma; asymptomatic apical periodontitis)

Definition

- Chronic apical periodontitis is an asymptomatic sequela of acute apical periodontitis (AAP) and is characterized radiographically by periapical radiolucent changes and histologically by the lesion dominated with macrophages, lymphocytes and plasma cells.
- The term *periapical granuloma* is a misnomer because the lesion is chronic inflammatory in composition and not a tumour. The term *granuloma* denotes *granulomatous* tissue, i.e. granulation tissue and chronic inflammatory cells infiltration in a fibrous connective tissue stroma.

Cause

Pulpal death followed by mild infection or irritation of periapical tissue that stimulates a productive cellular reaction.

Symptoms

- It is usually asymptomatic.
- Sometimes, patients may complain of mild pain on biting or chewing on solid food.
- In some cases, the tooth feels slightly elongated in its socket.

Diagnosis

- The involved tooth is usually nonvital and may be slightly tender on percussion. The percussion may produce a dull sound instead of a normal metallic sound because of the presence of granulation tissue around the root apex.
- Radiographically, thickening of periodontal ligament at the root apex and lack of continuity of lamina dura is seen initially. As proliferation of granulation tissue and concomitant resorption of bone continue, the periapical granuloma appears as a radiolucent area of variable size seemingly attached to the root apex. In some cases, this radiolucency is a well-circumscribed lesion, definitely demarcated from the surrounding bone. Sometimes, a thin radiopaque line or zone of sclerotic bone is seen outlining the lesion. (This indicates that this periapical lesion is a slowly

progressive lesion probably not undergone any acute exacerbation.)
- Vitality tests: Negative response.

Histopathology (fig. 9.2)

- Periapical granuloma consists of inflamed granulation tissue surrounded by a fibrous connective tissue wall.
- The granulation tissue demonstrates a variably dense lymphocytic infiltrate that is intermixed with neutrophils, plasma cells, histiocytes and less frequently mast cells and eosinophils.
- When numerous plasma cells are present, scattered eosinophilic globules of gamma globulin (Russell bodies) and clusters of lightly basophilic particles (pyronine bodies) may be seen.
- Rarely, epithelial rests of Malassez may be identified within the granulation tissue.
- The peripheral bone is usually lined by osteoclasts with few areas of bone resorptions.
- Sometimes, the root surface may show external root resorption due to cementoclastic activity or hypercementosis due to cementoblastic activity.

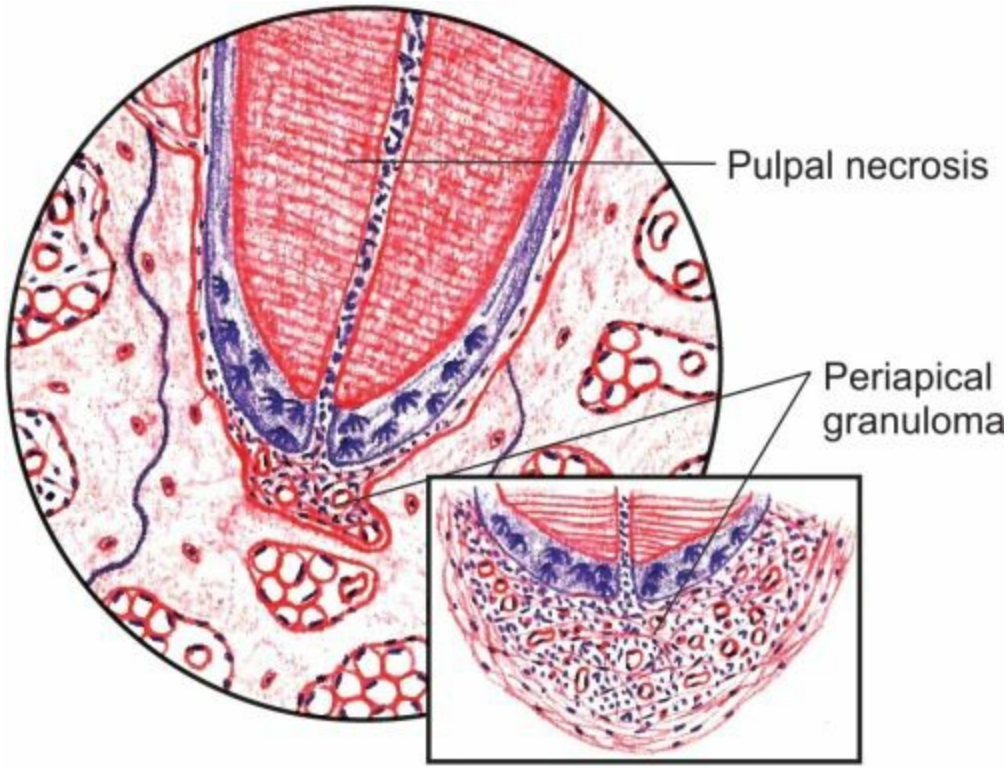


FIG. 9.2 Periapical granuloma.

Differential diagnosis

Periapical osteofibrosis: It is associated with vital tooth and requires no endodontic treatment.

Treatment

Root canal therapy.

Prognosis

The prognosis for long-term retention of the tooth is excellent.

Chronic periapical abscess

(Synonym: Chronic suppurative apical periodontitis)

Definition

A chronic alveolar abscess is a long-standing, low-grade infection of the periradicular alveolar bone characterized by the presence of an abscess draining through a sinus tract.

Causes

- Pulp death with extension of the infection into periapical region.
- It may be sequela of acute alveolar abscess.

Symptoms

- Usually asymptomatic and is elicited during routine radiographic examination or presence of sinus tract.
- The sinus tract usually prevents exacerbation or swelling by providing continual drainage of the periradicular lesion.

Diagnosis

- Involved tooth will be mildly painful, if there is blockage of sinus tract by coagulum. In such cases, the term *subacute periapical abscess* can be used.
- Radiograph often shows a diffuse area of bone rarefaction which blends with the normal bone. Periodontal ligament space is widened. Later, area of diffuse radiolucency around apex of the tooth is seen. It may vary from minor lesion to massive bone loss. External root resorption is commonly seen.
- Patient may give history of sudden, sharp pain that has subsided and not recurred, or may give a history of traumatic injury.
- Clinical examination may show a cavity, a composite or metallic restoration, or a jacket crown under which the pulp may have died without causing symptoms.
- Negative response to electric or thermal pulp tests.

Histopathology

- As infective process extends to the periapical tissues, some of the periodontal ligament fibres at root apex are detached or lost, followed by destruction of apical periodontal ligament. The apical cementum may also become affected.
- Lymphocytes and plasma cells are found at periphery of the abscess and variable number of PMN cells is seen at the centre.
- Fibroblasts may form a capsule at the periphery.
- Sinus tracts are generally lined with granulation tissue. In addition, acute and chronic inflammatory cells infiltration may be seen. The sinus tract ultimately heals by granulation following the elimination of infection in the root canal.

Differential diagnosis

It should be differentiated by periapical osteofibrosis or cementoma or ossifying fibroma, which is associated with a vital tooth and require no endodontic treatment.

Treatment

- Root canal therapy.
- Periradicular surgery is rarely indicated.

Prognosis

It depends on proper cleaning, shaping and obturation of the root canals. In addition, other factors such as the periodontal status, restorative needs and functional potential help to determine the prognosis.

Acute exacerbation of chronic lesions

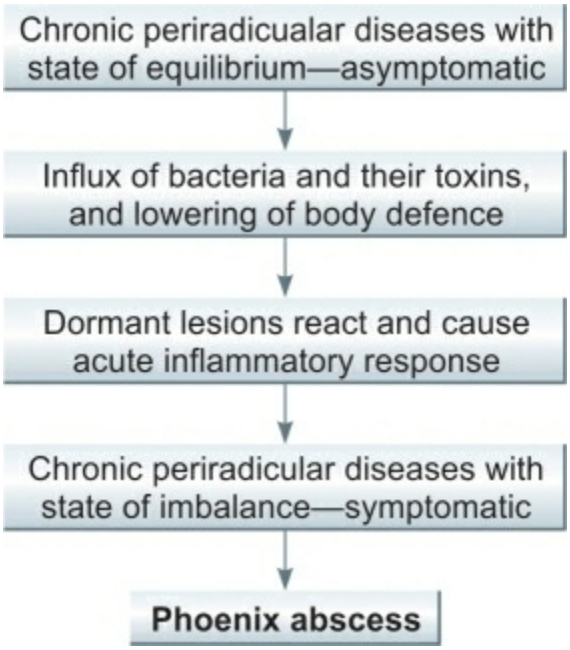
(Synonyms: Phoenix abscess; recrudescent abscess)

Definition

- It is an acute inflammatory reaction superimposed on an existing chronic lesion such as abscess, granuloma or cyst.
- Phoenix was an ancient bird that was reborn from its own ashes. In endodontics, it refers to the periapically infected tooth, which remanifests acute abscess symptoms after a prolonged dormant phase.

Pathogenesis

Pathogenesis of phoenix abscess is illustrated in Flowchart 9.2.



FLOWCHART 9.2 Pathogenesis of phoenix abscess

Naidorf (1985) postulated that facultative anaerobes such as *Bacteroides melaninogenicus*, which has been isolated from these teeth, begin to flourish and multiply when oxygen is introduced.

Symptoms

- Initially, tooth may be tender to percussion.
- As inflammation progresses, tooth may be elevated from its socket, and then becomes sensitive.
- The mucosa over periapical region may appear red and swollen and is sensitive to palpation.

Diagnosis

- The patient gives history of past episodes of pain and swelling, which has subsided and presently reappeared.
- Radiographs show well-defined periradicular radiolucent lesions.
- Tooth elicits lack of response to electric and thermal tests.

Histopathology

The areas of liquefaction necrosis with disintegrating PMN leukocytes and cellular debris (pus) are observed. These areas are surrounded by infiltration of macrophages and few lymphocytes and plasma cells.

Note: An abscess usually formed as a result of microbial infection in the periapical region is known as *sterile abscess* because it is devoid of bacteria, except for transient bacteria.

Differential diagnosis

- Acute alveolar abscess: It can be differentiated through proper patient's history and radiographs. It usually shows radiolucent bone rarefaction rather than well-defined radiolucency.
- Acute irreversible pulpitis: A tooth with acute irreversible pulpitis responds to a pulp vitality tests, whereas tooth with chronic lesions does not respond.

Treatment

Establishment of drainage and relieving systemic symptoms followed by endodontic therapy is suggested.

Prognosis

Good, once the symptoms have subsided.

Periapical cyst/cystic apical periodontitis/radicular cyst

It is discussed in Chapter 5 Cysts of the Oral and Maxillofacial Regions.

Osteomyelitis

Definition

Osteomyelitis is defined as an inflammation of the soft tissue components of the bone which includes bone marrow, haversian canals and periosteum with secondary changes of the mineralized components of the bone.

Classification

Based on the time of onset of the disease

- Acute osteomyelitis: It develops within 2 weeks after disease onset.
- Subacute osteomyelitis: It develops within one to several months after disease onset.
- Chronic osteomyelitis: It develops after a few months after disease onset.

Based on clinical presentation

- Suppurative osteomyelitis
 - Acute suppurative osteomyelitis
 - Chronic suppurative osteomyelitis
- Nonsuppurative osteomyelitis
 - Chronic sclerosing osteomyelitis
 - Focal
 - Diffuse
 - Garre's sclerosing osteomyelitis
 - Actinomycotic osteomyelitis
 - Tuberculosis osteomyelitis
 - Syphilitic osteomyelitis
 - Fungal osteomyelitis (mucormycosis and coccidioidomycosis)
 - Radiation osteomyelitis and necrosis

Based on mode of onset and specificity of the causative microorganisms

- Acute osteomyelitis: Most commonly nonspecific lesions are encountered in this category.
 - Acute suppurative osteomyelitis
 - Acute subperiosteal osteomyelitis
 - Acute periosteitis
- Chronic osteomyelitis
 - Nonspecific type

- Chronic intramedullary osteomyelitis
- Chronic focal sclerosing osteomyelitis
- Chronic diffuse sclerosing osteomyelitis
- Chronic osteomyelitis with proliferative periostitis
- Chronic subperiosteal osteomyelitis
- Chronic periostitis

- Specific type
 - Tuberculosis osteomyelitis
 - Syphilitic osteomyelitis
 - Actinomycotic osteomyelitis
 - Radiation-induced osteomyelitis
 - Idiopathic osteomyelitis

Pathogenesis

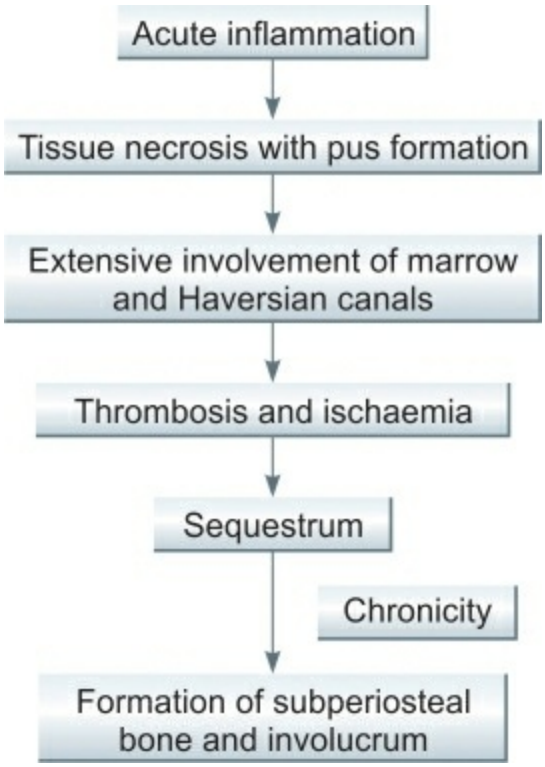
Predisposing factors

- Local factors: Trauma and road traffic accidents, splints, gunshot wounds.
- Systemic factors: Diabetes, agranulocytosis, leukaemia, severe anaemia, malnutrition, chronic alcoholism, sickle cell disease and febrile illnesses such as typhoid and viral infections.
- Conditions altering vascularity of bone: Radiation, Paget's disease of bone, osteopetrosis, bone malignancy and bone necrosis caused by chemicals.

Aetiological factors

- Direct spread of infection from dental pulp into jaw bone
- Spread of infection into bone from the pre-existing suppurative infections like periapical abscess, periodontal abscess, infected fractured jaw bone, acute necrotizing ulcerative gingivitis, pericoronitis, etc.
- Post-extraction infections
- Jaw bone fractures
- Gunshot injuries in the jaw with soft tissue lacerations and exposure of bone
- Post-radiation secondary infection
- Secondary infection in a pre-existing bone disease, e.g. Paget's disease, osteopetrosis, etc.
- Phosphorus poisoning
- Idiopathic factors

Pathogenesis of osteomyelitis is illustrated in Flowchart 9.3.



FLOWCHART 9.3 Pathogenesis of osteomyelitis

Microbiology of osteomyelitis

- **Infants (<1 year)**
 - Group B streptococci
 - *Staphylococcus aureus*
 - *Escherichia coli*
- **Children (1–16 years)**
 - *Streptococcus aureus*
 - *Streptococcus pyogenes*
 - *Haemophilus influenzae*
- **Adults (>16 years)**
 - *Staphylococcus epidermidis*
 - *Streptococcus aureus*
 - *Pseudomonas aeruginosa*
 - *Serratia marcescens*
 - *E. coli*

Acute suppurative osteomyelitis

Definition

It is a serious sequelae of periapical infection that often results in a diffuse spread of infection throughout the medullary spaces with subsequent necrosis of a variable amount of bone.

Clinical features

- **Age.** Usually occurs after 30 years of age (due to increased probability of systemic diseases and reduced bony resistance to infection).
- **Gender.** Male predilection.
- **Location.** The mandible is involved more often than the maxilla because it is a dense bone with thicker cortical plates and a limited blood supply. The mandibular lesions are usually diffuse in nature, while the maxillary lesions are mostly well localized.
- **Signs and symptoms**
 - Acute suppurative osteomyelitis often causes severe throbbing, deep seated pain. It manifests as a diffuse large swelling of the jaw and related soft tissues.
 - Loosening and soreness of the regional teeth is often seen.
 - The overlying soft tissue is erythematous, swollen and tender on palpation.
 - Excessive muscle oedema may lead to difficulty in mouth opening and swallowing.
 - Multiple intraoral or extraoral pus discharging sinuses are seen. Discharge of pus can also be seen from the gingival crevice or socket of the affected teeth.
 - Regional lymph nodes are enlarged and tender on palpation.
 - Paraesthesia or anaesthesia of the lip (either on affected side or the entire lip) is a common feature.
 - Patients are usually febrile with general symptoms like fever, malaise, anorexia and vomiting, etc.

Radiographic features

- Radiographic changes become more apparent after 1–2 weeks of the disease onset.
- It is characterized by large area of radiolucency in the jaw with ill-defined, moth-eaten margins.
- Sequestra are frequently seen as radiopaque foci of diminished radiodensity within the lesion. The sequestra become more sharply defined as they are gradually separated from the normal bone.

Histopathology (fig. 9.3)

- The medullary spaces of bone are usually occupied by inflammatory exudates.
- The inflammatory cell infiltrations predominantly contain PMN leukocytes with few lymphocytes and plasma cells.
- Some areas of the affected bone show complete necrosis with degeneration of both osteoblasts (bordering the bony trabeculae) and osteocytes (inside the lacunae) along with increased osteoclastic resorption, which often produces scalloping of the bony margins and result in the development of sequestrum.
- Sequestrum is a dead or necrosed fragment of bone, which is separated from the remaining viable bone.
- Sequestrum gradually undergoes spontaneous resorption or it may exfoliate through mucous membrane or skin.
- When the sequestrum becomes surrounded by new vital bone, the mass of enclosed nonvital bone is called *involucrum.*

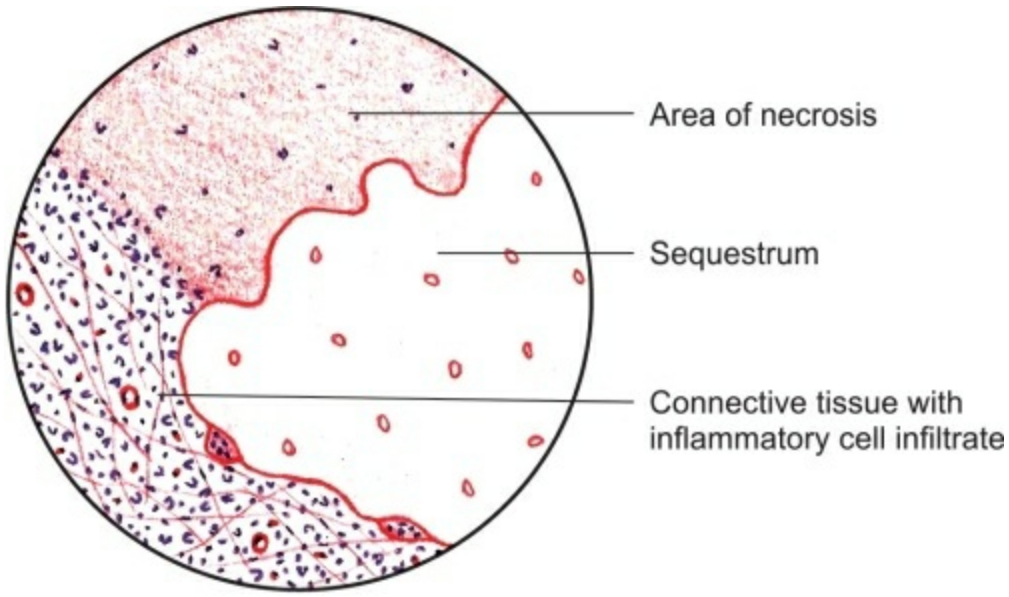


FIG. 9.3 Osteomyelitis.

Differential diagnosis

- Metastatic tumour in the bone with secondary infection.
- Primary intra-alveolar carcinoma.
- Intraosseous salivary gland neoplasm.

Prognosis and predictive factors

- Incision and drainage of the inflammatory exudates and pus.
- Antibiotic therapy.
- Removal of the sequestrum.
- Elimination of the primary source of infection, e.g. offending tooth.

Chronic suppurative osteomyelitis

- Chronic suppurative osteomyelitis may arise de novo or as a sequelae of acute suppurative osteomyelitis.
- It is generally believed that lower levels of virulence of the causative microorganisms are mostly responsible for the development of chronic suppurative osteomyelitis.

Clinical features

- **Age.** >30 years.
- **Gender.** Male predilection.
- **Location.** Posterior region of the mandible.
- **Signs and symptoms**
 - The pain is usually mild and dull in nature even if the disease is very extensive.
 - Jaw swelling is a common feature but mobility of teeth and sinus tract formations, etc are rare.
 - Rarely, sinus tracts may develop both intraorally and extraorally with intermittent discharge of purulent materials.
 - Anaesthesia and paraesthesia of the lip are very uncommon.
 - Acute exacerbations of the chronic disease may also occur.
 - Sequestrum is often found, which protrudes from the ulcerated skin or mucosal surfaces.

Radiographic features

Four different patterns are seen, which are as follows:

1. An ill-defined radiolucency in the bone with ragged borders.
2. Radiolucency with multiple radiopaque foci within it, the later structures represent sequestra.
3. A dense zone of radiopacity with faint radiolucency at the margin.
4. A 'salt and pepper' radiographic effect in the bone.

Histopathology

- Chronic inflammatory reaction in the bone with accumulation of exudates and pus within the medullary spaces.
- The lymphocytes, plasma cells and macrophages predominate among the inflammatory cells.
- Parallel osteoblastic and osteoclastic activity with the formation of irregular bony trabeculae having reversal lines.
- Sequestrum may develop in the later stages of the disease.

Differential diagnosis

- Metastatic tumour in the bone with secondary infection.
- Primary intra-alveolar carcinoma.
- Intraosseous salivary gland neoplasm.

Prognosis and predictive factors

- Administration of antibiotics after bacterial culture and sensitivity testing.
- Surgical intervention to remove the sequestrum (saucerization of the bone).

Chronic focal sclerosing osteomyelitis

(Synonym: Condensing osteitis)

Definition

Chronic focal sclerosing osteomyelitis is a rare nonsuppurative inflammatory condition of bone characterized by sclerotic bone formation around the root apex of a nonvital tooth.

Pathogenesis

- The condition develops as a result of chronic persistent inflammation in the bone, either due to high tissue resistance against infection or due to low virulence of the infective organisms.
- A low-grade inflammation in the jaw bone causes stimulation of the osteoblast cells, which results in the formation of dense trabecular bone in the area and this process is known as *osteosclerosis.*
- Osteosclerosis with additional bone formation may sometimes result in decreased marrow spaces.

Clinical features

- **Age.**<20 years.

- **Gender** Male predilection.
- **Location.** Posterior region of the mandible.
- **Signs and symptoms**
 - It is usually asymptomatic and no bony expansion is seen.
 - Sometimes mild pain is elicited.
 - Majority of the lesions are discovered incidentally during routine radiographic examination of the jaw bone.
 - Usually, associated tooth will be nonvital.

Radiographic features

- Well-circumscribed radiopaque mass with uniform radiodensity is seen around the root apex of a nonvital tooth.
- There is no radiolucent border around the lesion (as may be seen in cemento-osseous dysplasia).
- The affected tooth exhibits widening of periodontal ligament space.
- A residual area of condensing osteitis that is seen after resolution of the inflammatory focus is known as *bone scar*.

Histopathology

- Dense mass of bony trabeculae with little interstitial marrow tissue is seen.
- The osteocytic lacunae appear empty.
- The bony trabeculae exhibit many reversal and resting lines giving pagetoid appearance.
- If interstitial soft tissue is present, it is generally fibrotic and infiltrated only by small numbers of lymphocytes.

Differential diagnosis

- Cementoma or cementoblastoma
- Complex odontoma
- Metastatic tumour

Prognosis and predictive factors

- The affected tooth should be treated endodontically or it should be removed.
- No treatment required for the bony lesion.
- Biopsy may be necessary to rule out metastatic malignancy.

https://t.me/RoyalDentistryLibrary/

Chronic diffuse sclerosing osteomyelitis

Definition

Diffuse sclerosing osteomyelitis is a condition analogous to the focal form of the disease and also apparently represents a proliferative reaction of the bone to a low-grade infection.

Aetiology

- It is a proliferative reaction in response to a low-grade inflammation or infection in the jaw bone.
- The infections are usually widespread or diffuse in nature and are derived either from the periodontal tissue or the periapical tissue.
- These infections are usually subclinical in nature. Investigators have identified two bacteria in association with this disease, namely *Propionibacterium acnes* and *Peptostreptococcus intermedius*.

Clinical features

- **Age.** >50 years.
- **Gender.** No sex predilection.
- **Location.** Edentulous mandibular jaws.
- **Signs and symptoms**
 - It is usually asymptomatic but sometimes the patients may complain of a vague pain in the jaw with foul taste in the mouth.
 - Acute exacerbation may occur in the lesion, which often produces mild pain, suppuration and fistulas tract formation, etc.
 - SAPHO (synovitis, acne, palmoplantar pustulosis, hyperostosis and osteitis) syndrome: It is a special entity characterized by chronic multifocal osteomyelitis with hyperostosis and osteitis of the bone. The condition is associated with negative bacterial culture and is nonresponsive to antibiotic therapy.

Radiographic features

- Radiograph shows areas of diffuse or nodular sclerosis of the bone.
- The appearance may be similar to the 'cotton-wool' radiopacities seen in Paget's disease of bone.
- The border between the sclerotic bone and the normal bone is not well demarcated.

https://t.me/RoyalDentistryLibrary/

Histopathology

- Dense, irregular trabeculae of bone, some of which are bordered by an active layer of osteoblasts.
- Focal areas of osteoclastic activity are sometimes seen.
- The bone in some lesions shows a pronounced 'mosaic pattern' indicative of repeated periods of resorption followed by repair.
- The soft tissue between the individual trabeculae is fibrous and shows proliferating fibroblasts and few capillaries as well as small focal collections of lymphocytes and plasma cells. PMN cells may be present, if the lesion is in an acute exacerbation phase.
- In some lesions, the inflammatory component is completely reduced leaving only sclerotic bone and fibrosis.

Differential diagnosis

- Paget's disease of bone
- Osteopetrosis
- Cementomas

Prognosis and predictive factors

- No treatment is required as the disease is often asymptomatic and is too extensive for surgical removal.
- In case of acute exacerbations, surgical debridement and removal of the sequestrum are done along with antibiotic therapy.

Chronic osteomyelitis with proliferative periostitis

(Synonym: Garre's osteomyelitis)

Definition

It is a distinctive type of chronic osteomyelitis in which there is focal gross thickening of the periosteum with peripheral reactive bone formation resulting from mild irritation or infection.

This condition was first authentically reported in 1893 by a German physician named C. Garre.

Pathogenesis

- Predisposing factors
 - Chronic periapical abscess
 - Chronic periapical granuloma with secondary infection

https://t.me/RoyalDentistryLibrary/

- Infected periapical cyst
- Perifollicular infection in an erupting tooth or impacted tooth
- Chronic periodontal infection
- Chronic infections of the soft tissues overlying the jaw
- Mechanical irritation in the jaw from dentures

- It is usually believed that a low-grade, sustained infection or inflammation of the jaw bone, which is occurring in a young person with high degree of body resistance and excellent tissue reactivity, may often cause Garre's osteomyelitis.
- Generally in Garre's osteomyelitis, a low-grade chronic inflammation spreads through the cortical bone of the jaw and it initiates a proliferative reaction in the periosteum, leading to subperiosteal new bone formation.

Clinical features

- **Age.** <20 years.
- **Gender.** No sex predilection.
- **Location.** Posterior part of the mandible.
- **Signs and symptoms**
 - The involved jaw bone often presents a grossly carious, nonvital tooth (mostly first permanent molar tooth).
 - There is thickening and swelling of the affected bone with little or no pain.
 - The size of the swelling may be ranging from few centimetres to the entire length of the mandible.
 - Occasionally, slight tenderness or a vague pain may be felt in the affected area of bone.
 - The overlying skin and oral mucosa appear normal.
 - Slight pyrexia and moderate leukocytes may be present but the erythrocyte sedimentation rate (ESR) is normal.

Radiographic features

An occlusal radiograph shows a focal overgrowth of bone on the outer surface of the cortex and exhibits many concentric or parallel opaque layers (duplication of the cortical bone) which often produce a typical 'onion skin' appearance.

Histopathology

- Supracortical but subperiosteal mass is composed of much reactive new

https://t.me/RoyalDentistryLibrary/

bone and osteoid tissue with many trabeculae.

- These trabeculae are arranged either parallel to each other or in a retiform pattern or they are oriented perpendicular to the cortex.
- The connective tissue between the bony trabeculae is rather fibrous and shows a diffuse or patchy distribution of lymphocytes and plasma cells.

Differential diagnosis

- Ossifying fibroma
- Ewing's sarcoma
- Osteoblastic osteosarcoma

Prognosis and predictive factors

- Elimination of the causative agent.
- Extraction of the offending tooth and antibiotic therapy.
- The cortical swelling undergoes spontaneous physiologic remodelling and does not require any additional surgical intervention.

Note: Periosteal new bone formation or neoperiostosis may occur in a variety of other conditions like infantile cortical hyperostosis (Caffey's disease), hypervitaminosis A, syphilis, leukaemia, Ewing's sarcoma, metastatic neuroblastoma and even a fracture callus.

External resorption

It is discussed in Chapter 12 Regressive Alterations of the Teeth.

Comparison between pulpal and periapical diseases is given in Table 9.2.

https://t.me/RoyalDentistryLibrary/

Table 9.2

Pulpal and periapical diseases

	Pain	Vitality tests	Radiographs
Reversible pulpitis	Mild	Reversible sensitivity to cold	No change
Acute pulpitis	Severe, constant	Hyperresponse to none	No change
Chronic pulpitis	Mild, intermittent	Reduced response	No change
Acute periapical abscess	Severe, pain on percussion	No response	No change
Periapical granuloma	None to slight	No response	Lucency
Periapical cyst	None to slight	No response	Lucency

Key points

- *Reversible pulpitis* is a mild-to-moderate inflammatory condition of the pulp caused by noxious stimuli in which the pulp is capable of returning to the uninflamed state following removal of the stimuli.
- *Irreversible pulpitis* is a persistent inflammatory condition of the pulp, symptomatic or asymptomatic, caused by a noxious stimulus.
- *Chronic hyperplastic pulpitis* is a productive pulpal inflammation due to an extensive carious exposure of a young pulp. This disorder is characterized by the development of granulation tissue, is covered at times with epithelium and results from long-standing, low-grade irritation.
- *Acute apical periodontitis* is a painful inflammation of the periodontium as a result of trauma, irritation or infection through the root canal regardless of the vitality of pulp.
- *Acute periapical abscess* is a localized collection of pus in the alveolar bone at the root apex of a tooth following death of the pulp with extension of the infection through apical foramen into the periradicular tissues.
- *Periapical granuloma* is asymptomatic sequelae of acute apical periodontitis (AAP) and is characterized radiographically by periapical radiolucent changes and histologically by the lesion dominated with macrophages, lymphocytes and plasma cells.
- *Chronic alveolar abscess* is a long-standing, low-grade infection of the periradicular alveolar bone characterized by the presence of an abscess draining through a sinus tract.
- *Phoenix abscess* is an acute inflammatory reaction superimposed on an

https://t.me/RoyalDentistryLibrary/

existing chronic lesion such as abscess, granuloma or cyst.

- *Osteomyelitis* is defined as an inflammation of the soft tissue components of the bone which includes bone marrow, haversian canals and periosteum with secondary changes of the mineralized components of the bone.
- *Garre's osteomyelitis* is a distinctive type of chronic osteomyelitis in which there is focal gross thickening of the periosteum with peripheral reactive bone formation resulting from mild irritation or infection.

Frequently asked questions

1. Sequelae of diseases of dental pulp and periapical tissues.
2. Microbiology of disease of dental pulp and periapical tissues.
3. Chronic hyperplastic pulpitis.
4. Classify diseases of periapical tissues and add a note on acute periapical abscess.
5. Periapical granuloma.
6. Phoenix abscess.
7. Write classification, pathogenesis, clinical features, radiographic features and histopathology of acute suppurative osteomyelitis.
8. Garre's osteomyelitis.

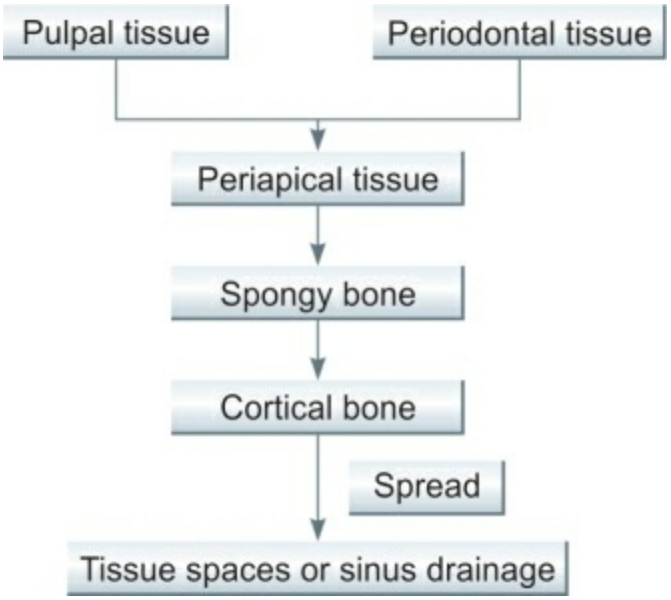
https://t.me/RoyalDentistryLibrary/

CHAPTER 10

https://t.me/RoyalDentistryLibrary/

Spread of oral infection

- An infective process involving the tooth and its supporting structures is known as *odontogenic infections*.
- Oral infections may originate either from periodontal or pulpal tissues (Flowchart 10.1).
- The odontogenic infections may spread through lymphatics, bloodstream or directly through the tissues.
- Factors affecting the ability of the infection to spread depend on the type and virulence of the organisms, general health of the patient, the anatomical site of the initial infection and patient's immune mechanism.



FLOWCHART 10.1 Origination of oral infections

Cellulitis

(Synonym: Phlegmon)

Definition

It is a diffuse inflammation of soft tissues which is not circumscribed or confined to one area but which, in contrary to the abscess, tends to spread

https://t.me/RoyalDentistryLibrary/

through tissue spaces and along facial planes.

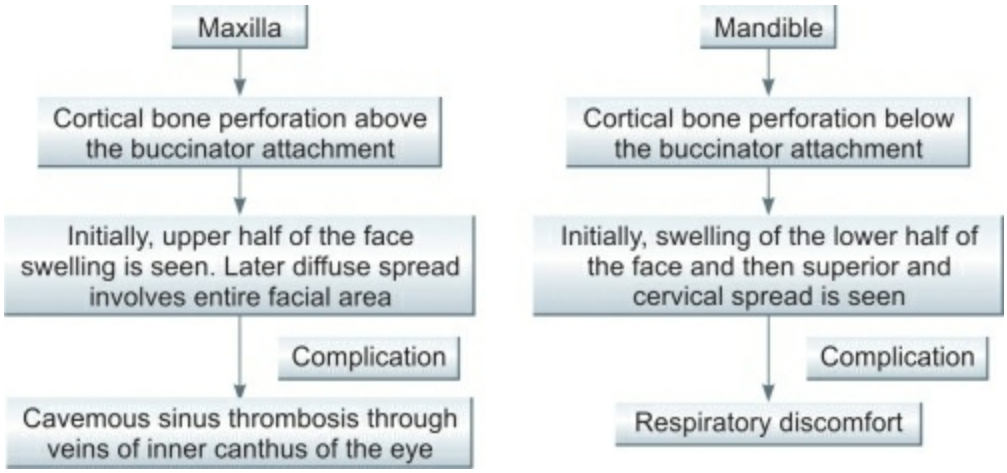
Pathogenesis

- It is due to microorganisms that produce significant amount of streptokinase, hyaluronidase and fibrinolysin, which act to breakdown or dissolve hyaluronic acid, intercellular cementing substances and fibrin. This process helps in rapid spread of infection.
- Usually, streptococci consume local oxygen and metabolize nutrients and create an acidic environment conducive for anaerobic bacteria such as *Prevotella* and *Porphyromonas* species, which destroy collagen.
- Source of infection: Dental infections (apical abscess, osteomyelitis), periodontal infection, pericoronitis, dental extractions, infected needles and jaw fractures.

Clinical features

- The patient will be moderately ill and have elevated temperature.
- Firm, painful swelling of the soft tissues is seen.
- Swelling may be in superficial or deeper planes.
 - Superficial tissue space infections: The overlying skin will be inflamed, hard, indurated, highly painful and has an orange peel appearance. A severe type of cellulitis that does not undergo suppuration proceeds towards rapid inflammatory infiltrate of subcutaneous tissue. The skin appears bluish due to tissue cyanosis. Such fast-spreading cellulitis is called *phlegmon*.
 - Deeper tissue space infections: The overlying skin will be in normal colour and regional lymphadenopathy is usually present.
- It may involve either maxilla or mandible (Flowchart 10.2).

https://t.me/RoyalDentistryLibrary/



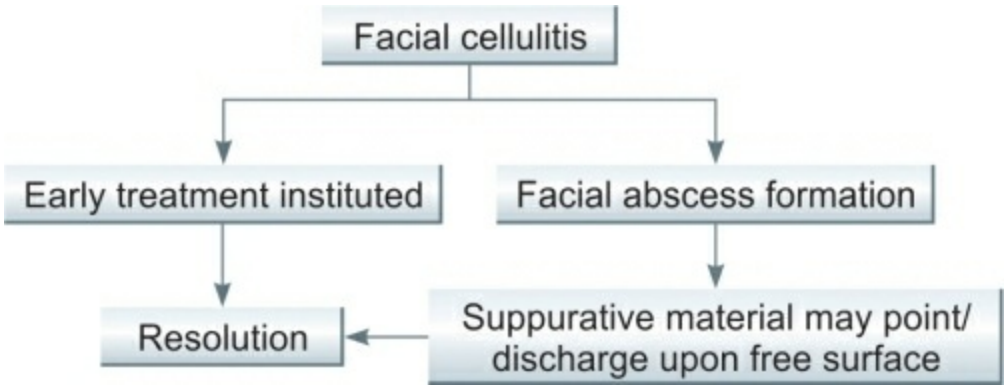
FLOWCHART 10.2 Involvement of maxilla and mandible in cellulitis

Histopathology

- It usually presents nonspecific diffuse acute inflammatory reaction.
- Diffuse exudation of polymorphonuclear lymphocytes and occasional lymphocytes, with considerable serous fluid and fibrin, causes separation of connective tissue or muscle fibres.

Prognosis and predictive factors (flowchart 10.3)

- The administration of antibiotics and the removal of cause are necessary.
- To avoid the further spread of infection or solidification of abscess, the patient should be advised not to massage the affected area with any medication.



FLOWCHART 10.3 Prognosis of cellulitis

https://t.me/RoyalDentistryLibrary/

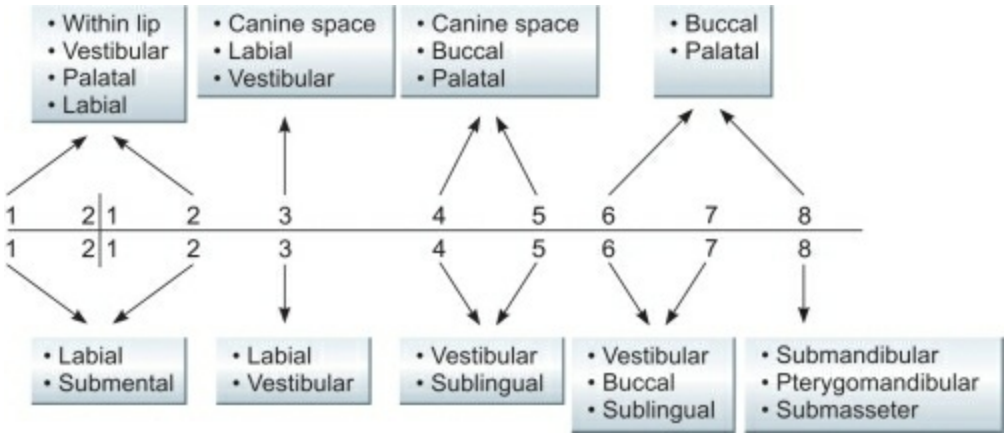
Mandibular and maxillary tissue spaces

Definition

- Tissue spaces or facial spaces are potential spaces situated between planes of fascia that form natural pathways along which infection may spread, producing a cellulitis, or within which infection may become localized with the actual abscess formation.
- Normally, these facial spaces contain salivary gland, fat or lymph nodes.
- Drainage of spaces occurs by perforation of a bony plate (usually of thin cortex) along the lines of least resistance. The attachment of muscles also determines the route that infection will take, channelling the infection into certain tissue spaces.

Classification

Classification of tissue spaces is given in Tables 10.1–10.3 and Flowchart 10.4.



FLOWCHART 10.4 Spread of infection from maxillary and mandibular teeth

Table 10.1

Classification of tissue spaces in maxillofacial region

Primary		**Secondary**	
Directly relate to teeth (e.g. canine space infection)		• Not directly related to teeth • They are referred as *secondary spaces* since they are infected after involvement of primary spaces • Failure to treat a primary space infection or a compromised host results in secondary space involvement	
Mandible	**Maxilla**	*Mandible*	*Maxilla*
Submental	Canine fossa	Sublingual	Within lips
Submandibular	Buccal space	Submasseter	Maxillary antrum
Buccal space	Infratemporal space	Parotid	Palatal
		Pterygomandibular	Subperiosteal
		Pharyngeal	Subtemporal
In relation to mandible		**In relation to maxilla**	
Submental space		Within the lip	
Submandibular space		Canine fossa	
Sublingual space		Palatal subperiosteal interval	
Buccal space		Buccal space	
Submasseteric space		Maxillary antrum	
Parotid space		Infratemporal space	
Pterygomandibular space		Subtemporalis muscle interval	
Pharyngeal space			
Peritonsillar space			

Table 10.2

Tissue spaces in relation to mandible

Space infection	Boundaries	Infection	Signs and symptoms
Submental space	It extends from the anterior border of the submaxillary space to the midline and it is limited in depth by the mylohyoid muscle	• Infection arising from lower incisors, lower lip and chin • Tip of the tongue, floor of mouth	• It presents as an anterior swelling in the submental area • The patient as classical ptotic chin (double chin appearance) • The overlying skin appears board like with taut swollen area • It causes extreme pain during swallowing • It may also cause dyspnoea
Sublingual space	*Superior:* Mucosa of the floor of the mouth *Inferior:* Mylohyoid muscle *Anterior and lateral:* Body of the mandible *Posterior:* The hyoid bone *Medial:* Median raphe of the tongue	• Infections, arising from apical or periodontal disease of the incisors or canine teeth frequently, pass directly into this space • Fracture of mandible can also lead to sublingual haematoma followed by the infection • The infection may arise directly from perforation of lingual cortical plate above mylohyoid attachment or by extensions by other spaces, primarily the submaxillary space	• It produces an obvious swelling in the floor of the mouth, displacing the tongue to the opposite side • It may lift the tongue in case of bilateral space infection and push it against the palate; it may also cause dyspnoea • The mucosa appears shiny, firm and painful
Submandibular space	• It is a space medial to the mandible and below the posterior portion of the mylohyoid muscle *Medial:* The hyoglossus and digastric muscles *Lateral:* The superficial fascia and skin • It encloses submaxillary salivary glands and lymph nodes	• The commonest source of infection comes from the mandibular molars • Other sources include lymph node and submandibular gland	• It is one of the most commonly involved facial and cervical tissue spaces. The abscess is triangular in shape, obliterates the angle of the mandible, beginning at the lower border of the mandible and extending to the level of hyoid bone • It can spread to submaxillary gland and nodes because of close anatomic proximity resulting in sialadenitis and lymphadenitis
Buccal space	*Lateral:* Skin and subcutaneous tissues of the face *Medial:* Buccinator muscle and its covering buccopharyngeal fascia *Anterior:* Posterior border of the zygomatic major muscle above; depressor anguli oris below *Posterior:* The anterior edge of the masseter muscle *Superior:* Zygomatic arch *Inferior:* Lower border of the mandible	• Posterior maxillary teeth are the source of most buccal space infections • It results when infection erodes through bone superior to attachment of buccinator muscle	• Swelling begins at the lower border of the mandible, extends till the zygomatic arch • It is dome-shaped, and the periorbital oedema develops due to impaired, venous and lymphatic drainage • Trismus is not usually present
Submasseteric space	• It is a space located over the surface of ramus of mandible below the masseter muscle • The posterior boundary of this space is parotid gland, and anteriorly it adjoins the retromolar fossa	It arises due to pericoronal infection from the impacted mandibular third molars	• Patient has severe trismus and pain and there may be facial swelling also • The abscess never points intraorally or extraorally • The patient is often seriously ill • Long-standing cases may lead to osteomyelitis of mandible
Parotid space	• Space formed by splitting of investing layer of deep cervical fascia to enclose parotid gland • The space contains parotid gland and all its associated structures	• Secondary infections from lateral pharyngeal space or by retrograde extension along the parotid duct • Infection may also spread to temporal fossa	• Smooth painful swelling in front and below the external ear • Fever, chills usually present • Patient does not exhibit trismus
Pterygo-mandibular space	The space between the medial side of the mandible and the medial pterygoid muscle *Medially:* Medial pterygoid muscle *Laterally:* Medial surface of ramus of the mandible *Superiorly:* Lateral pterygoid muscle *Posteriorly:* Deep lobe of parotid gland *Inferiorly:* Attachment of medial pterygoid to the mandible *Anteriorly:* Pterygomandibular raphe	• Secondary infection may spread from the sublingual and submandibular spaces to this space • Pericoronitis of mandibular third molars, injection of the maxillary tuberosity with an infected needle or solution	• Severe trismus and limiting jaw movements are seen • Extreme radiating pain is present • Severe pain on jaw movements • Minimal swelling on examination • Fetid odour, dysphagia is present • The area is tender on palpation with the discharge of pus in the infected area
Peritonsillar space (Quinsy)	It is a localized infection in the connective tissue space of the faucial tonsil and the superior constrictor muscle of the pharynx	• It is not a very common odontogenic infection presented • Usually from the pericoronitis associated with lower third molars	• Severe dysphagia, bulk in throat, changed in speech is the frequent complaints • Displacement of soft palate and uvula to opposite side is present
Lateral pharyngeal space	It is one of the parapharyngeal spaces *Anterior:* The buccopharyngeal fascia, parotid gland and pterygoid muscle *Posterior:* Prevertebral fascia *Lateral:* Carotid sheath *Medial:* Lateral wall of pharynx	• Mandibular third molars • Also from adjacent Pterygomandibular space infection or from the sublingual, submandibular space infection	• The most prominent features include pyrexia, malaise, dehydration and pain on deglution with lesser degree of trismus • The pain may also refer to ear • It can also spread to retropharyngeal space on invade carotid sheath

Table 10.3

Tissue spaces in relation to maxilla

Space infection	Boundaries	Infection	Signs and symptoms
Canine space	It presents between the levator anguli oris and the levator labii superioris muscles	• Involvement is primarily due to maxillary canine tooth infection • Long root allows erosion through the alveolar bone of the maxilla	• Obliteration of the nasolabial fold • Superior extension can involve lower eyelid
Palatal space	It is the collection of pus between mucoperiosteal flap and palatal bone	Periodontal and periapical infection from any maxillary tooth most frequently from maxillary lateral incisors and infection via palatal roots of maxillary molars	It presents as a classical well-circumscribed, soft, fluctuant, tender swelling on the affected side of the palate
Infratemporal space	It is located posterior to the maxilla *Medial:* Lateral plate of the pterygoid process of the sphenoid bone *Superior:* Skull base *Lateral:* Portion of the ramus and coronoid process *Anteriorly:* Maxillary tuberosity *Posterior:* Lateral pterygoid muscle, the condyle and the temporal muscle	• Maxillary molar infections (more so with distoangular third molar), injection into the space with infected needles • Most commonly as sequelae of pterygomandibular space infection	• Trismus is the key presentation • Along with the painful swelling on the area • The entire cheek may be swollen • On mouth opening, the jaw deviates to the affected side • The involvement of pharynx may cause dysphagia and severe pain or feeling of pressure in the area of infection

Ludwig's angina

Definition

- It is a severe type of cellulitis, beginning usually in the submaxillary space and secondarily involving the sublingual and submental spaces.
- All three submandibular spaces (submandibular, sublingual and submental spaces) must be involved to consider it as true Ludwig's angina.

Pathogenesis

- Infection originates from either periapical or periodontal infections of the mandibular molars, from the penetrating injury of the floor of the mouth such as gunshot or stab wound, or from osteomyelitis in a compound fracture.
- The rapid production of tissue-spreading enzymes like streptokinase, hyaluronidase, urokinase and fibrinolysin, spreads the infection to ipsilateral sublingual space.
- This infection crosses over to the opposite sublingual space and then to the opposite submandibular space.

- The infection then rapidly spreads to submental space either by direct extension across the mylohyoid muscle or by lymphatic spread.
- Microflora: Nonspecific mixed infection. Streptococci are usually isolated, also there are staphylococci, gram-negative enteric organisms like *E. coli* and *Pseudomonas*, and anaerobes like *Bacteroides* and *Peptostreptococcus*. Others like *Fusospirochetal organisms, Bacteroides oralis, B. melaninogenicus* are also isolated.

Clinical features

- The involvement of all these spaces occurs within 24–48 hours.
- The patient is extremely ill with elevated temperature, rapid pulse, fast respiration, dehydration, dribbling saliva from the open mouth.
- There is rapidly developing swelling of the floor of the mouth that might extend up to clavicles, the overlying swelling is taut, shiny and erythematous with stiff neck.
- The swelling is firm, painful and diffuse, showing no evidence of localization and paucity of pus.
- There is difficulty in eating and swallowing as well as in breathing.
- Intraorally, there is elevation of tongue leading to progressive dyspnoea.
- **Complications**
 - As the disease progresses, oedema of glottis may occur leading to death by suffocation.
 - Cavernous sinus thrombosis followed by meningitis may be sequelae to this infection.

Prognosis and predictive factors

- Proper hydration with IV fluids and high dose of antibiotic therapy with immediate surgical decompression.
- Extraction of the offending tooth is done at the earliest.
- Emergency tracheotomy is done to prevent suffocation.

Cavernous sinus thrombosis

Definition

- It is a serious condition consisting of formation of thrombus in the cavernous sinus or its communicating branches.
- It is a rare but life-threatening intracranial complication of odontogenic

origin.

Pathogenesis

- Infections of the head, face and intraoral structures above the maxilla are prone to produce this disease.
- The area of upper lip, commissures and lower lip is often called *dangerous area* as the infection from this area rapidly spreads to cavernous sinus through anterior facial vein.
- Route of infection is given in Table 10.4.
- **Microbiology:** The most frequent pathogens are *Staphylococcus aureus, S. albus* and streptococci. Others like *Proteus, Pseudomonas, Pneumococcus, Haemophilus* along with other anaerobic organisms can also cause this disease.

Table 10.4

Route of infection of cavernous sinus thrombosis

Facial or angular vein (external route)	Ptreygoid plexus (internal route)
• This is the most common route • It carries infections from the face and lip • Spread of infection is very rapid with a short fulminating course because of the large, open system of veins	• Dental infections are carried through this route • Spread of infection is slower, because of small, twisting passages

Clinical features

- It can occur at any age group.
- Patients are extremely ill. Persistent headache may be present. Nausea, pain, chills and fever may be complained.
- The characteristic exophthalmos with oedema of eyelids, chemosis, paralysis of extraocular muscles, along with impairment of vision is seen.

Prognosis and predictive factors

- A combination of intravenous antibiotics, anticoagulants and surgery is the optimal treatment.
- The primary site of infection may require early drainage, especially when acute sinusitis is the cause of infection.
- The disease may be fatal as a result of brain abscess or meningitis.
- The use of antibiotics has decreased its mortality, but the condition is still serious with a mortality rate of up to 30%.

Maxillary sinusitis

Definition

- It is defined as the acute or chronic inflammations of the maxillary sinus.
- It is the inflammation of the mucous membrane of the maxillary sinus.

Pathogenesis

- Direct extension of odontogenic infection, usually from the upper premolar or molar teeth.
- Broken root fragments of any of these teeth may be pushed into the sinus along with some bacteria.
- Others factors like common cold, influenza, exanthematous disease may also cause this disease.
- It may be due to local spread from adjoining frontal and paranasal sinuses.
- Foreign bodies, tumours, granulomatous lesions of nasomaxillary lesions may also cause maxillary sinusitis.
- **Microflora:** *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*.

In children, gram-negative bacilli, anaerobic organisms, rhinovirus and parainfluenza viruses are most commonly isolated. If secondary to dental infection, microorganisms are same as those associated with the dental infection.

Classification and its manifestations

Classification of maxillary sinusitis and its manifestations are described in Table 10.5.

Table 10.5

Classification of maxillary sinusitis and its manifestations

Features	Acute	Chronic
Aetiology	It results from an acute periapical abscess or acute exacerbations of a chronic inflammatory periapical lesion, which involves the sinus through direct extensions	It may develop as the acute lesion subsides or may represent a chronic lesion from the onset
Microflora	*S. pneumoniae, H. influenzae* and *M. catarrhalis*	Anaerobes and *Streptococcus, Bacteroides* or *Veillonella*
Clinical features	• Moderate to severe constant and localized pain • Pressing over maxilla increases the pain • Pain referred to cheek, posterior teeth and ear • Pain increases when the patient bends over or is supine position • Patient may complain of a discharge of pus into nose and fetid breath • General symptoms like sweating, chills, fever, dizziness and nausea and at times dyspnoea are also present	• Symptoms generally lacking and the condition may be discovered only during routine examination • Sometimes headache, fever, vague facial pain, stuffy sensation of the affected face is present • There may be mild discharge of pus into nose and a fetid odour • Children may have purulent rhinorrhoea, persistent cough and fever • Rarely, antrolith may be detected radiographically
Diagnosis	Clinical signs and symptoms, transillumination, sinus view radiograph, computed tomography	Clouding of sinus on radiograph
Histopathology	• Maxillary sinus lining showing typical acute inflammatory infiltrate with oedema of the connective tissue and often haemorrhage • Squamous metaplasia may occur sometimes	• Thickening of mucosal lining and development of polyps (hyperplastic granulation tissue) with lymphocytic and sometimes plasma cell infiltration is seen • These polyps tend to fill the sinus and obliterate it
Treatment	• Removal of cause of the disease • Patient is advised to maintain a good oral hygiene • Antibiotic coverage	• Removal of cause of the disease • Antibiotic coverage

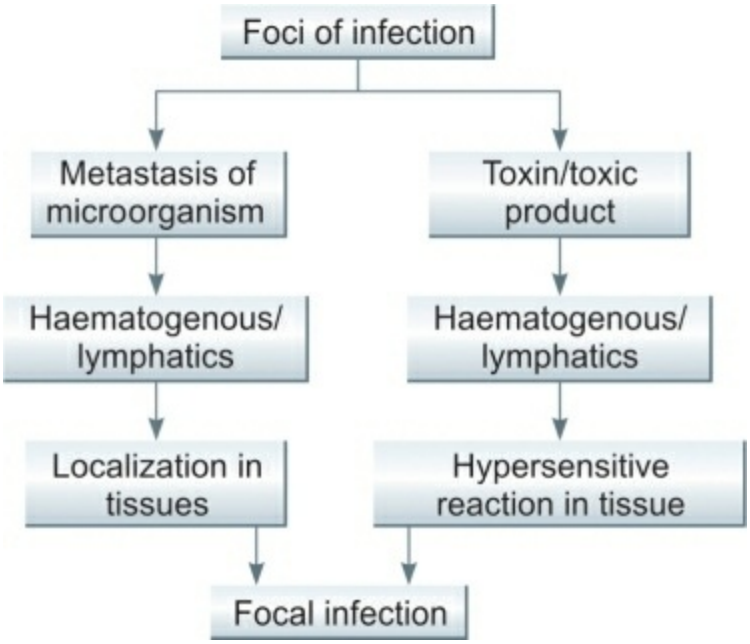
Focal infection

Definition

- It is a localized or generalized infection caused by the dissemination of microorganisms or toxic products from a focus of infection.
- Foci of infection: It refers to a circumscribed area of tissue, which is infected with exogenous pathogenic microorganisms and is usually located near a mucous or cutaneous surface.

Pathogenesis

Pathogenesis of focal infection is given in Flowchart 10. 5.



FLOWCHART 10.5 Pathogenesis of focal infection

Oral foci of infection

- There are many situations in the oral cavity that can cause distant metastases. They include infected periapical lesions such as granulomas, cysts, abscesses and teeth with infected root canals.
- Periodontal diseases, osteomyelitis and infected root fragments.

Significance of oral foci of infection

- Several life-threatening systemic diseases can occur due to either direct spread of infections or dissemination of toxins liberated by the oral pathogenic microorganisms into the bloodstream or lymphatics.
- Following are few examples of these diseases caused by focal infections from the oral and orofacial infective sources:
 - Rheumatoid arthritis and rheumatic fever
 - Subacute bacterial endocarditis
 - Cavernous sinus thrombosis
 - Meningitis and brain abscess
 - Ocular diseases
 - Gastrointestinal diseases
 - Upper respiratory diseases
 - Skin diseases: Acne, seborrhoea dermatitis, tinea, eczema, dermatitis venenata, impetigo, scabies, urticaria, psoriasis and pityriasisrosea

- Renal diseases

Key points

- *Cellulitis* is a diffuse inflammation of soft tissues which is not circumscribed or confined to one area but which, in contrary to the abscess, tends to spread through tissue spaces and along facial planes.
- Ludwig's angina is a severe type of cellulitis, beginning usually in the submaxillary space and secondarily involving the sublingual and submental spaces.
- *Cavernous sinus thrombosis* is a serious condition consisting of formation of thrombus in the cavernous sinus or its communicating branches.
- *Maxillary sinusitis* is defined as the inflammation of the mucous membrane of the maxillary sinus.
- *Focal infection* is a localized or generalized infection caused by the dissemination of microorganisms or toxic products from a focus of infection.
- *Foci of infection:* It refers to a circumscribed area of tissue, which is infected with exogenous pathogenic microorganisms and is usually located near a mucous or cutaneous surface.

Frequently asked questions

1. Clinical manifestations of mandibular/maxillary space infections
2. Discuss pathogenesis and clinical manifestations of Ludwig's angina
3. Focal infection

CHAPTER 11

Physical and chemical injuries of the oral cavity

Injuries of teeth associated with tooth preparation

Injuries to teeth particularly dentine and pulp are caused not only due to dental caries, but also due to procedures needed for repair of lesions involving dental hard tissues.

Effect of tooth preparation

- Tooth preparation is usually done by rotary instruments such as stainless steel burs, tungsten carbide burs and diamond burs. Sometimes, laser and air abrasion are also used alternatively.
- Pulpal responses depend on:
 - Heat generated by friction
 - Cutting of odontoblastic process
 - Drying of dentinal tubules
 - Thickness of remaining dentine
 - Vibrations
 - Removal of minerals
 - Exposure of the organic matrix of dentine
 - Formation of smear layer

Reaction to rotary instrumentation

- Stainless steel burs are commonly used for crown and cavity preparation.
- As the enamel hardness is too high, these burs could not abrade instead they cut or chip away the tooth material.
- Moreover, a considerable amount of pressure is applied during the procedure, which results in excessive heat production and evaporation of the dentinal tubule contents.
- Following three general reactions to cavity preparation are noted:
 1. Production of secondary dentine
 2. Changes in the odontoblasts associated with injured tubules
 3. General changes in the pulp
- In mild reactions:

- The odontoblasts become distorted and get reduced in number.
- Small vacuoles may appear between them, probably lymph exudates.
- Capillaries may become prominent.

- In severe injuries:
 - Complete disorganization and haemorrhage in the odontoblastic layer.
 - More infiltration of injured locus by polymorphonuclear (PMN) cells and lymphocytes.
- More serious injuries cause open cavities due to sudden exposure of more number of dentinal tubules to oral fluids and bacteria.

Note: Dentine has a heat dissipating action, which reduces the temperature rise within the pulp. The low thermal conductivity of dentine helps it to act as an effective insulating medium.

High-speed instrumentation

- Presently, high-speed rotary instruments with tungsten carbide and diamond burs are commonly used for cavity or crown preparation.
- Bernier and Knapp observed the following mild pulpal changes during high-speed instruments (100,000 rpm) cavity preparation:
 - Alteration in ground substance
 - Oedema
 - Fibrosis
 - Odontoblastic disruption
 - Reduced predentine formation

Effect of air abrasive techniques

- In this technique, aluminium oxide under pressure is used as an abrasive for cavity preparation and surface treatment.
- The main drawback of this procedure is, it does not allow the operator to control the depth of cutting and also the abrasive dust is a potential health hazard to the clinician as well as the patient.
- Nowadays, it is used only to clean the pits and fissures prior to the application of sealants.

Effect of ultrasonic technique

- Ultrasonic equipment have been advocated, as they cause less heat, noise and vibrations.
- It involves conversion of electrical energy into mechanical energy in the form of vibration of a tiny cutting tip (≈29,000 vibrations/second with amplitude of 0.0014 inch) and results in a rapid reduction of the tooth substance.
- Mild hyperaemia, haemorrhage and a slight neutrophilic and lymphocytic infiltration are seen in the pulp tissue immediately below the cut dentinal tubules.
- After a few weeks, irregular secondary dentine deposition is seen.

Light amplification by stimulated emission of radiation (LASER)

- It is an electro-optical device, which upon stimulation can convert light waves into an intense, concentrated, uniform, narrow beam of monochromatic light with an energy source of greater intensity and exceptional flexibility.
- The radiation may be continuous or modulated or short pulses.
- Carbon dioxide and neodymium: yttrium–aluminium–garnet (Nd:YAG) lasers are the most commonly used.
- The main problem with laser cutting of hard dental tissue is generation of heat and forbidden tactile control.
- Lasers are used in dental practice for following purposes:
 - To coalesce deep pits and fissures.
 - To desensitize the exposed root surfaces.
 - To make the hard tissue surface rough to promote bonding as an alternative to acid etching.
 - To vapourize the carious tissue.
 - To vapourize the organic tissues in the root canal during endodontic procedures.

Effect of heat

- Extraordinary amount of heat produced by cutting and grinding instruments used in tooth preparation is an important clinical problem.
- Temperature above 700°F has been recorded on the cutting surface of bur.
- Tissue reaction may be mild, severe or more severe, depending upon the following factors:

- The size, shape and composition of the bur or stone
- The speed of the bur or stone
- The amount and direction of pressure applied
- The amount of moisture in the field of operation
- The length of time that the bur or stone is in contact with the tooth
- The type of tissue being cut

- The constant application of water during tooth preparation will prevent many complications.

The effect of various restorative materials on dental tissues

Zinc oxide eugenol

- It is used routinely as a temporary filling material or a root canal sealant.
- It is least injurious of all filling materials to the dental pulp.
- Eugenol of this cement fixes cells, depresses cell respiration and reduces neural transmission.
- It exerts a palliative and sedative effect on the mildly damaged pulp as it inhibits synthesis of prostaglandins and leukotrienes.

Zinc phosphate cement

- It is widely used as a protective base for restoration of deep cavities, cementing cast inlays, crowns and other restorations.
- Its significant deleterious effects on the pulp have been reported mainly due to phosphoric acid.
- It causes hyperaemia or haemorrhage with inflammatory cell infiltration of the pulp accompanied by reduction in the size and number of the odontoblasts.

Silver amalgam

- It is used as a filling material for shallow and deep cavities.
- Any damage to the pulp will be due to leakage around the restoration, not due to filling material itself.
- If deep amalgam restorations are not properly insulated, then it causes thermal shock.
- Dark-coloured metallic components of the silver alloy discolour the

dentine dark grey and tooth may appear discoloured.
- The contact with gingiva causes inflammatory reaction due to corrosion products.

Glass ionomer cement

- Most widely used as a restorative and lining material.
- It is the most biocompatible restorative material.
- Biocompatibility of glass ionomer cement is due to weak nature of polyacrylic acid.
- Histologically, there is minimal or no inflammation in pulp.
- Cervical cavities may lead to mild pulpal pain for short period of time after restoration, probably due to increased dentine permeability after acid etching.

Physical injuries of hard tissues

Physical injuries of teeth

Bruxism

(Synonym: Night grinding)

- Bruxism is the habitual grinding or clenching of the teeth either during sleep or as an unconscious habit during waking hours.
- It is the most common sleeping disorder.

Aetiology

It includes:

- Local factors
- Systemic factors
- Psychological factors
- Occupational factors

Local factors

- Mild occlusal disturbances and tensions.
- An unconscious attempt to establish a greater number of teeth in contact or to counteract a local irritating situation.
- In children, this habit is associated with the transition from the deciduous to the permanent dentition and may result from an unconscious attempt to place the tooth planes so that musculature will be at rest.

Systemic factors: Gastrointestinal disturbances, subclinical nutritional deficiencies, allergic and endocrinal disturbances.

Psychological factors

- Anxiety, stress and emotional tensions.
- When person suffers from fear, rage, rejection or a variety of emotions hidden in the subconscious state.

Occupational factors

- Athletes and watchmakers are commonly prone to suffer from bruxism.
- Voluntary bruxism develops in people who habitually chew gum, tobacco, pencils or toothpicks.

Clinical features

- The typical grinding or clenching motions during sleep or waking hours may lead to symptomatic effects, which are divided into six major categories:
 1. Effects on dentition
 2. Effects on periodontium
 3. Effects on masticatory muscles
 4. Effects on temporomandibular joints
 5. Headache
 6. Psychologic and behaviour effects
- When the habit is firmly established, severe wearing or attrition of the teeth is seen which may cause generalized sensitivity.
- Usually, occlusal facets are seen.
- Facial pain and headache are commonly present.
- As the bruxism continues, loss of integrity of the periodontal structures or loosening or drifting of teeth or gingival recession with alveolar bone loss is seen.
- Temporomandibular joint disturbances will be evident.
- Hypertrophy of the masticatory muscles, particularly masseter muscle is seen.
- Trismus and alteration in opening and closing pattern of the jaws are seen.

Prognosis and predictive factors

- If the underlying cause is emotional, then nervous factor must be corrected.
- Removable splints may be constructed to immobilize the jaws or to guide the movement, so that the periodontal damage is minimal.

- Recently, botulinum toxin (Botox) injection into the masseter muscle has been very successful in treating the grinding and clenching of bruxism.

Fractures of teeth

Tooth fracture is a common injury among young children.

Aetiology

- Most commonly due to sudden trauma.
- It may be due to a fall, a blow or an automobile accident.
- Weakened tooth due to large restoration, internal resorption and root canal treatment are more susceptible for fracture.

Clinical features

- **Age.** Any age, but children are more prone to injury.
- **Gender.** Male predilection.
- **Location.** Maxillary anterior teeth are commonly affected.

Classification of teeth fractures as given by ellis (fig. 11.1)

- *Class 1:* Simple fracture of the crown, involving enamel with little or no dentine.
- *Class 2*: Extensive fracture of the crown, involving considerable amount of dentine but not the dental pulp.
- *Class 3:* Extensive fracture of crown, involving dentine with dental pulp exposure.
- *Class 4:* Traumatized tooth becomes nonvital, with or without loss of crown structure.
- *Class 5:* Teeth lost as a result of trauma.
- *Class 6:* Fracture of root, with or without loss of crown structure.
- *Class 7:* Displacement of tooth, without fracture of crown or root.
- *Class 8:* Fracture of crown en masse and its replacement.
- *Class 9:* Traumatic injuries to deciduous teeth.

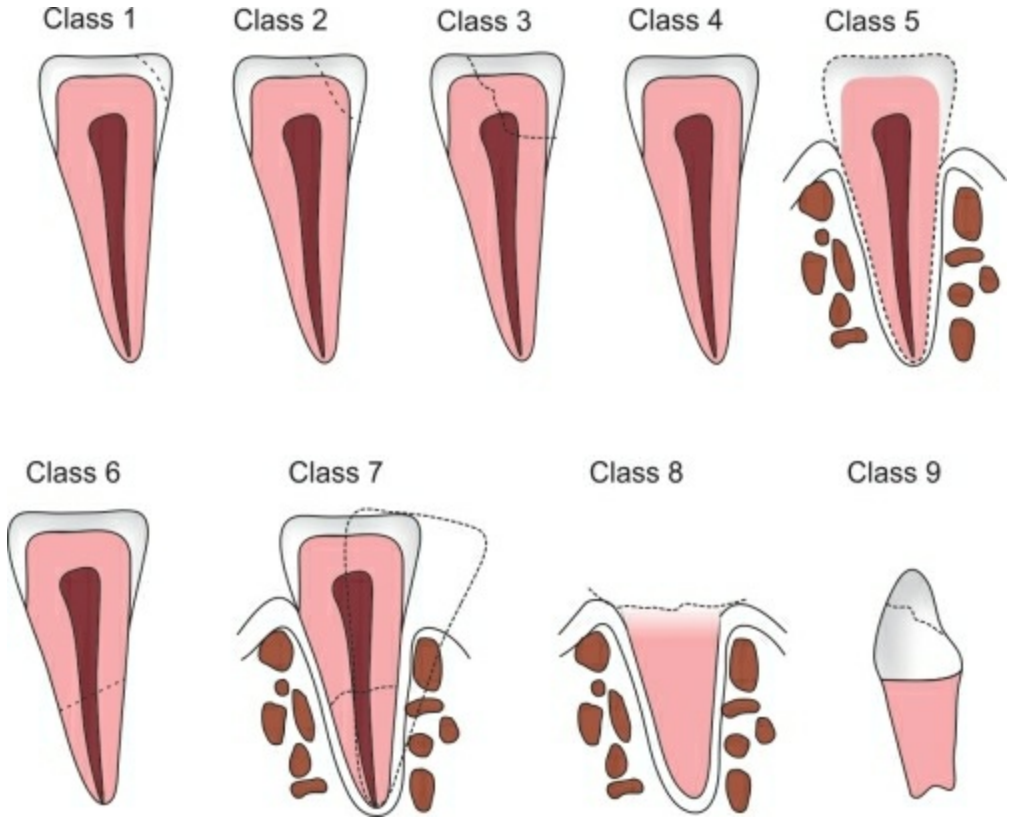


FIG. 11.1 Classification of teeth fractures—by Ellis.

The clinical manifestations, treatment and prognosis of the fractured tooth depend upon involvement of pulp and the root.

Root fractures

- **Age.** 10–20 years.
- **Gender.** Male predilection.
- **Location.** It involves mostly middle third of the root.
- **Signs and symptoms**
 - Tooth will be mobile and painful.
 - Displacement of the coronal portion of the tooth is commonly seen.
 - Commonly, tooth becomes nonvital.
 - Sometimes, it may get repaired by formation of reparative dentine along the pulp wall and cementum on the outer surface of the root.

Histopathology

- The most satisfactory form of healing is the union of the two fragments by calcified tissue.
- The clot between the root fragments is organized and this connective tissue is subsequently the site of new bone or cementum formation.

- If the apposition between two fragments is not close, then union occurs mainly by connective tissue alone.

Injuries to the supporting structures of the tooth (fig. 11.2)

Concussion

It is caused by an injury which is not strong enough to cause serious, visible damage to the tooth and the periodontal structures. On clinical examination, the tooth may be mobile or displaced from its original position. Treatment includes selective grinding and elimination of occlusal forces.

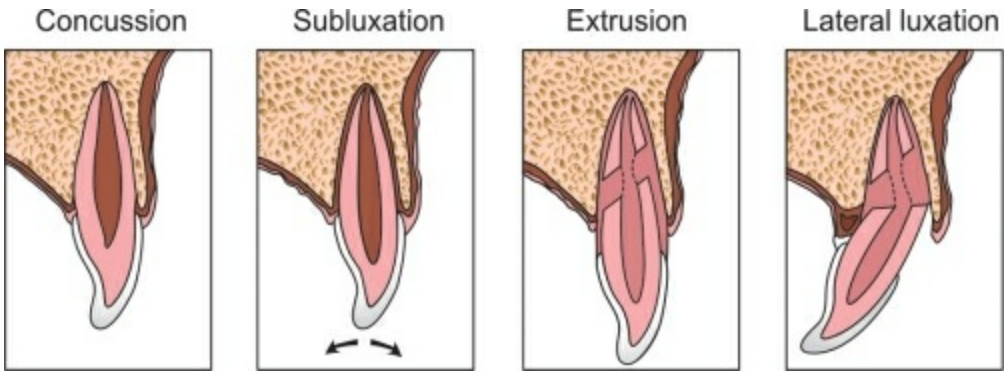


FIG. 11.2 Injuries to the supporting structures of tooth.

Subluxation

It refers to abnormal loosening of the tooth without displacement due to sudden trauma. Tooth is mobile on palpation and sensitive to percussion and occlusal forces. Rupture of periodontal tissue is usually evident by bleeding at the gingival marginal crevice. Later, tooth becomes nonvital due to severance of apical blood supply.

Avulsion

It is dislocation of the tooth from its socket due to traumatic injury. It can be partial or total. Partial avulsion includes intrusion, extrusion, lateral luxation or displacement. Management is by repositioning of the tooth and stabilization by splints. Completely avulsed tooth can be replanted in its socket.

Tooth ankylosis

Generally, the term *ankylosis* refers to the union of two adjacent hard structures. Fusion between the tooth and bone is termed as *tooth ankylosis.*

Aetiology

- Occlusal trauma.
- Periapical inflammation.
- It is also seen among root canal treated teeth or replanted teeth.

Clinical features

- It is usually asymptomatic, unless there is a concomitant pulp infection.
- Tooth gives a dull muffled sound on percussion.
- It is noticed only during extraction of the tooth.

Radiographic features

- A thin radiolucent line around the root which represents the periodontal ligament will be absent.
- Mild sclerosis of the bone and apparent blending of the bone with tooth root is also evident.

Histopathology

- Area of root resorption which has been repaired by a calcified material, bone or cementum, is seen.
- The periodontal ligament is completely obliterated in the area of the ankylosis (Fig. 11.3).

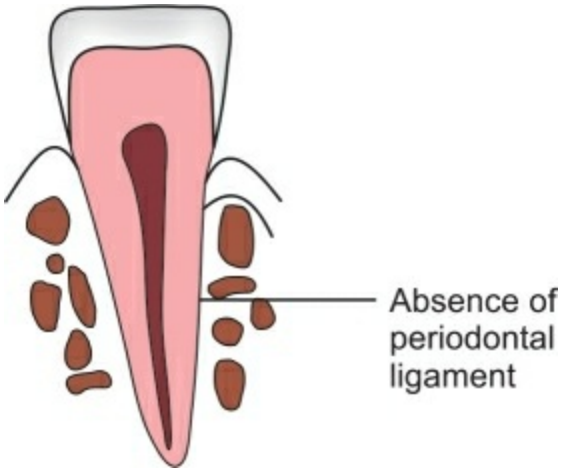


FIG. 11.3 Tooth ankylosis.

Prognosis and predictive factors

There is no treatment for ankylosis.

Physical injuries of the bone/fractures of bone

Fractures of the jaws

- Mandible is more prone for fractures, since chin is a prominent feature of the face.
- Fractures of the jaws are more common among men.
- Fractures of the craniofacial complex occur commonly due to automobile, industrial, sports accidents and fights.
- Fractures may be simple, greenstick, compound or comminuted.
 1. *Simple fracture:* The bone is broken completely and the overlying structures are intact and are not exposed to exterior.
 2. *Greenstick fracture:* Common in young, soft bones of infants and children. It is named so because of its similarity to a *greenstick*, which bends when partially broken.
 3. *Compound fracture:* External wound is associated with the break. It is common in road traffic accidents.
 4. *Comminuted fractures:* Bone is crushed or splinted and it may be exposed to exterior.

Fractures of the maxilla

- Maxillary fractures are more serious than the mandibular fractures.

- The most common causes are road traffic accidents, blow, fall and industrial accidents.
- Direction, force and the location of the impact determine the extent of fracture.
- *Le Fort's classification* is most commonly used for fractures of maxilla and surrounding structures.
 1. *Le Fort I fracture (horizontal fracture or floating fracture):* It is characterized by the separation of body of the maxilla from the skull base, below the level of zygomatic process.
 2. *Le Fort II (pyramidal fracture):* It is characterized by vertical fractures through the facial aspects of maxilla and extends upwards to the nasal and ethmoid bones and usually extends through the maxillary sinus.
 3. *Le Fort III (transverse fracture):* It is a high level fracture that extends across the orbits through the base of the nose and ethmoid region to the zygomatic arch. Orbital bone is fractured and its lateral rim is separated at the zygomaticofrontal suture. Zygomatic arch is fractured.

Clinical features

- Displacement
- Anterior open bite
- Swollen face
- Reddish eye due to subconjunctival haemorrhage
- Nasal haemorrhage
- Unconsciousness
- Cerebrospinal fluid rhinorrhoea
- Cranial nerve involvement

Fractures of the mandible

- Most common causes are road traffic accidents and physical violence.
- Most commonly involved sites are angle of the mandible, followed by condyle, molar region, mental region and symphysis.
- Displacement of the mandible depends on the direction of the fracture line, muscle pull and the direction of force.

Clinical features

- Pain during movement

- Occlusal derangement
- Abnormal mobility
- Gingival laceration
- Crepitus on movement
- Trismus
- Loss of sensation of the involved side
- Ecchymosis

Prognosis and predictive factors

Jaw fractures are treated by reduction and immobilization.

Traumatic cyst

(Synonyms: Solitary bone cyst; haemorrhagic cyst; unicameral bone cyst; simple bone cyst)

It is discussed in Chapter 5 *Cysts of the Oral and Maxillofacial Regions.*

Effects of orthodontic tooth movement (fig. 11.4)

- The science of orthodontics is based upon the ability of teeth to be moved through bone, without their subsequent extrusion or loss, by the application of pressure or tension under appropriate and controlled circumstances.
- Bone under pressure—resorption of bone

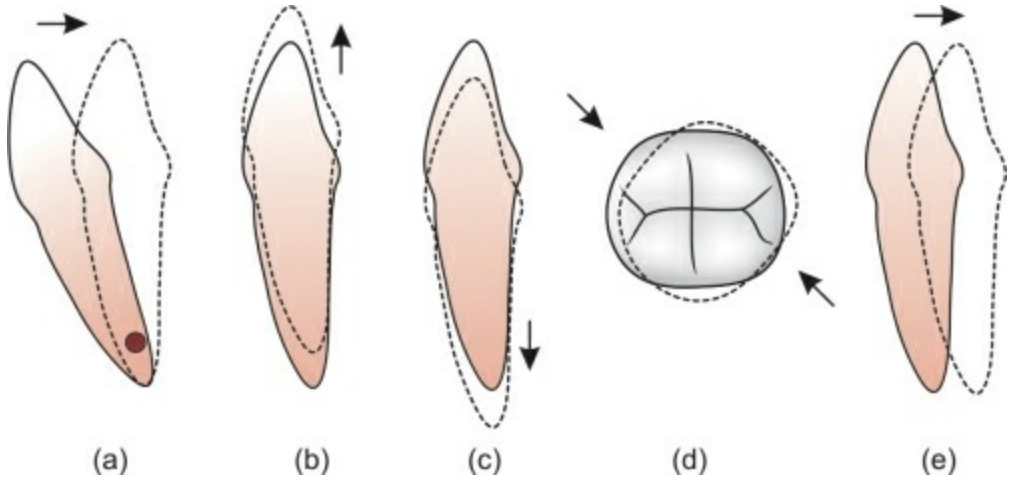


FIG. 11.4 Orthodontic tooth movements: (a) Tipping; (b) Extrusion; (c) Intrusion; (d) Rotation; (e) Translation.

Bone under tension—deposition of new bone

- The pressure or tension is applied on the periodontal ligament through orthodontic appliances.

Tipping

- The exact tooth movements and the position are assumed after application of orthodontic force.
- The initial reaction on the pressure side is a compression of periodontal ligament which, if excessive and prolonged, may result in ischaemia with hyalinization and/or necrosis of the tissue. On the opposite side (tension side), there may be actual tearing of the periodontal fibres and small capillaries with haemorrhage into the area.
- Usually, within a few hours or days, large number of osteoclasts appear along the surface of bone under pressure and resorption begins. This continues until the force of the pressure has been entirely dissipated.
- Initially, the new trabeculae of bone on the tension side become evident and later, thin elongated spicules with osteoblasting riming will be arranged parallel to periodontal fibres. As stabilization occurs, the alveolar bone gradually assumes its compact pattern.
- Deposition of new bony spicules on the outer surface of the labial plate is seen in instances of pressure in labial direction. This serves to maintain the thickness of thin labial plate and prevents its perforation by the tooth.

Note

Why resorption of compact bone occurs before resorption of cementum on tooth root?

Resorption of calcified tissues is favoured by the local vascularity. Bone of the alveolus is more vascular than cementum and tooth root, particularly since the ischaemia of the periodontal ligament adjacent to the cementum.

Why teeth of young individuals respond much more rapidly than do the teeth of older adults?

- Due to the differences in chemical constitution of bone.
- Variation in tissue reactivity and local vascularity.
- Degree of the stimulus needed to evoke this response shows difference between various age groups.

Extrusion

- It is similar to normal tooth eruption.
- It consists of apposition or deposition of new bony spicules at the alveolar crest and at the fundus of the alveolus, these spicules are arranged in a direction parallel to the direction of force.
- The direction of spicules then becomes parallel to long axis of the tooth and tends to increase the height of the alveolar crest.
- The normal width of the apical periodontal ligament is maintained by the new bone formation.

Intrusion

- The tissue changes in this type of orthodontic movement will be opposite to those found during extrusion or elongation.
- Resorption of bone occurs at the apical area and around the alveolar margins.
- New bone formation is minimal.

Rotation

Rotations are labial or lingual movements of a tooth around its long axis.

Translation

If the line of action of an applied force passes through the centre of resistance of a tooth, then all the points on the tooth will move an equal distance in the same direction signifying a bodily displacement.

The physical injuries of soft tissues

Linea alba

- It is a white line seen on the buccal mucosa extending from the commissures of lip along the level of occlusal plane.
- It is caused by physical irritation and pressure exerted by posterior teeth.
- It is usually bilateral and more prominent in people who have bruxism or clenching habit.
- Histologically, hyperkeratosis and intracellular oedema are seen.

Traumatic ulcer

(Synonym: Decubitus ulcer)

Aetiology

- These ulcers are caused by some forms of trauma, such as:
 - Biting of oral mucosa
 - Denture irritation
 - Toothbrush injury
 - Exposure of the mucous membrane to a sharp tooth or carious lesion
 - Injury due to external irritant
- The *cotton roll injury* is an iatrogenic injury; it is a common reaction when the dry cotton roll placed by the dentist is roughly removed and mucosa adhering to it is torn.

Clinical features

- Site: Most commonly on lateral border of the tongue followed by buccal mucosa, lips and occasionally the palate.
- It may be:
 - Acute form: Shorter duration
 - Chronic form: Longer duration
- Usually, injury heals rapidly and uneventfully.
- The lesion appears as areas of erythema surrounding a central removable, yellow purulent membrane. In some instances, lesion develops a rolled white border immediately adjacent to area of ulceration.
- Ulcers are small, painful and irregular in shape.

Histopathology

- Area of ulceration is covered by fibrinopurulent membrane that consists of fibrin intermixed with neutrophils.
- Adjacent epithelium will be normal or slightly hyperplastic and/or hyperkeratosis.
- Ulcer bed consists of granulation tissue with mixed inflammatory infiltrate.

Prognosis and predictive factors

- An obvious source of injury should be removed.
- Dicyclomine HCl or hydroxypropyl cellulose films can be applied for

temporary pain relief.

- If the cause is not obvious or if a patient does not respond to therapy, then biopsy is indicated to rule out chronic traumatic ulcer or carcinoma.

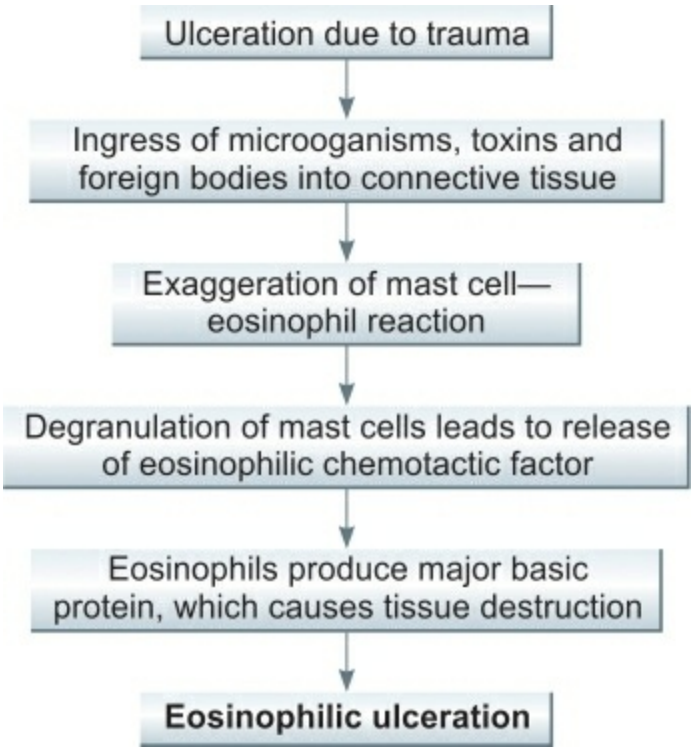
Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE)

(Synonyms: Eosinophilic ulceration; traumatic granuloma)

- TUGSE is a reactive, benign, asymptomatic, self-limiting lesion of the oral mucosa.
- Clinically, it may mimic squamous cell carcinoma.

Pathogenesis (flowchart 11.1)

- Unknown, but it may associate with trauma.
- Trauma may be due to malposed teeth or a partial denture.
- *Riga-Fede disease* occurs in infants between 1 week and 1 year of life. Lesions are usually observed on anteroventral surface of the tongue, caused by erupting mandibular incisors. These associated teeth are usually natal or neonatal teeth.
- *Atypical eosinophilic ulceration* is a rare lesion and exhibits sequential ulceration, necrosis and self-regression. It represents the oral counterpart of a cutaneous T cell lymphoproliferative disorder.
- It can be an initial finding in few neurologic conditions like familial dysautonomia, Lesch–Nyhan syndrome, Gaucher's disease, cerebral palsy and Tourette syndrome.



FLOWCHART 11.1 Pathogenesis of eosinophilic ulceration

Clinical features

- **Age.** Any age.
- **Gender.** Male predilection.
- **Location.** Anteroventral and dorsal parts of the tongue is gingiva, palate and mucobuccal fold.
- **Signs and symptoms**
 - It persists for few weeks to months.
 - The centre of the lesion is covered by a removable yellow fibrinopurulent membrane with erythematous borders.

Histopathology

- Area of ulceration is covered by fibrinopurulent membrane that consists of fibrin intermixed with dense and deeply infiltrative lymphoproliferation and massive eosinophilia.
- Presence of sheets of lymphocytes and histiocytes along with hyperplasia of the vascular connective tissue causes elevation of the surface ulceration.

Prognosis and predictive factors

- Even large eosinophilic ulcerations heal rapidly after biopsy.
- Though extraction of the involved teeth solves the problem in Riga-Fede disease; the teeth should be retained, if they are stable.

Lip biting and cheek biting

(Synonyms: Morsicatiolabiorum; morsicatiobuccarum)

Aetiology

These injuries may be habitual or psychogenic.

Clinical features

- Commonly seen among females than males.
- It involves biting, holding and tearing of the epithelium of labial mucosa, buccal mucosa, tongue and chewing of the cheeks or stripping of the epithelium or creating negative pressure by sucking the lips and cheeks.
- The lesions are usually bilateral and seen along the occlusal line and also on the vestibular surface of the lips.
- The mucosa appears white and shredded with erythematous areas.
- Ulceration is very common.

Histopathology

- Extensive areas of hyperkeratosis with keratin projections representing ragged areas are seen.
- Chronic inflammatory cell infiltration is seen in the areas of ulceration.

Prognosis and predictive factors

- Counselling and psychotherapy.
- Placement of acrylic shield will help in preventing teeth from causing injury.

Denture injuries

The oral mucosa is subjected to variety of injuries as a result of wearing partial and complete dentures and they include:

1. Traumatic ulcers
2. Generalized inflammation
3. Inflammatory fibrous hyperplasia

4. Inflammatory papillary hyperplasia
5. Allergy or intolerance to denture base

Traumatic ulcers

(Synonym: Sore spots)

Aetiology

- Overextension of the denture flanges.
- Sequestration of bony spicules under the denture.
- Roughened or high spot on inner surface of the denture.

Clinical features

- Single or multiple ulcers are commonly developed within a day or two after the insertion of a new denture.
- Ulcers are small, painful and irregular in shape, and are usually covered by a delicate grey necrotic membrane and surrounded by an inflammatory halo.

Histopathology

- Loss of continuity of surface epithelium with fibrinous exudates covering the exposed connective tissue.
- Proliferative activity of epithelium along the margins of the lesion is seen.
- In acute condition, PMN cells are infiltrated into the connective tissue beneath the area of ulceration.
- In chronic condition, the acute inflammatory cells are replaced with lymphocytes and plasma cells. Moreover, proliferation and dilatation of capillaries with prominent fibroblastic activity is seen.

Prognosis and predictive factors

Correction of underlying cause like relief of the flanges, high spots or removal of tiny sequestrum is recommended.

Generalized inflammation

(Synonyms: Denture sore mouth; denture stomatitis)

Aetiology

- The exact aetiology is unknown.
- It is not an allergic condition, since patch testing with denture material gives negative results.
- Parasitism by *Candida albicans* in association with denture trauma, poor oral hygiene habits and dietary and systemic alterations.
- Newton suggested that, it may be related to the 'sweat retention syndrome' in which keratin plug formation of the sweat glands or accessory salivary glands forces sweat or saliva into adjacent tissue with subsequent inflammation.

Clinical features

- Commonly seen in the maxilla.
- The mucosa beneath the denture becomes extremely red, swollen, smooth or granular and painful.
- Commonly, multiple pin point foci of hyperaemia are seen.
- Severe burning sensation will be present.

Prognosis and predictive factors

- Antifungal therapy.
- Correction of improperly or poorly fitting dentures.
- Maintaining good oral hygiene and cleanliness of dentures by soaking overnight in nystatin solution.
- Rebasing dentures with soft tissue conditioners.

Inflammatory fibrous hyperplasia

(Synonyms: Denture injury tumour; epulis fissuratum)

Aetiology

It is the most common tissue reaction to a chronic ill-fitting denture along the denture borders.

Clinical features

- This lesion is not restricted to any specific location, but it occurs in areas of chronic irritation such as gingiva, buccal mucosa and angle of the mouth.
- It is characterized by the development of elongated rolls of tissue in the mucobuccal or mucolabial folds.

- The excess fold of tissue is firm in consistency and is not usually inflamed.
- There may be irritation or even ulceration in the base of the fold into which the denture flange fits.

Histopathology

- The hyperplastic mass of tissue shows fibrous connective tissue covered by a variable thickness of stratified squamous epithelium.
- Pseudoepitheliomatous hyperplasia and hyperkeratosis are often seen.
- The connective tissue is composed chiefly of coarse bundles of collagen fibres with few fibroblasts, blood vessels and acute inflammatory cells.
- Mucopolysaccharide keratin dystrophy also referred as *plasma pooling* consists of homogenous, eosinophilic pools of material in the superficial spinous layer of epithelium. But its significance is still not known.

Prognosis and predictive factors

- Surgical excision.
- New dentures should be constructed.
- Old dentures can be rebased, repaired or replaced.

Inflammatory papillary hyperplasia

(Synonym: Palatal papillomatosis)

Aetiology

- Unknown aetiology.
- It is considered as a form of inflammatory hyperplasia associated with ill-fitting dentures, frictional irritation, poor oral hygiene or wearing denture continuously for 24 hours a day.
- *C. albicans* may be a contributing factor.

Clinical features

- **Age.** Any age.
- **Gender.** No sex predilection.
- **Location.** Commonly mucosa of the hard palate is involved.
- **Signs and symptoms**
 - It presents as numerous, closely arranged, red papillary projections almost involving the entire hard palate.
 - The individual papillae are over 1–2 mm in diameter.

- Tissue exhibits varying degree of inflammation and rarely ulceration.

Histopathology

- Numerous small vertical projections are seen.
- Each projection composed of parakeratotic or orthokeratotic stratified squamous epithelium and central core of connective tissue.
- In advanced cases, varying degree of pseudoepitheliomatous hyperplasia is seen.
- Connective tissue can vary from loose and oedematous to densely collagenous nature.
- Severe inflammatory cell infiltrates predominantly of lymphocytes and plasma cells are usually seen.

Prognosis and predictive factors

- Discontinuing the use of old ill-fitting dentures and construction of new dentures without surgical removal of excess tissue will lead to regression of oedema and inflammation.
- Sometimes, tissue conditioners can be used to rebase the old dentures.

Denture base intolerance or allergy

- True allergy to dental base material is extremely rare.
- Allergic reaction is mainly caused by sensitivity to the monomer of both regular and self-curing types.
- Plasticizers of denture soft liners are cytotoxic and affect many cellular metabolic reactions.
- Histopathologically, epithelial changes like acanthosis, hyperplasia or ulceration can be noted.

Radiation injuries

- The term *radiation* is applied to two different forms of energy:
 - Electromagnetic radiation
 - Particle radiation
- *Electromagnetic radiation* consists of a continuous spectrum of varying wavelengths ranging from long electrical waves down through infrared, visible light, ultraviolet, X-rays, gamma rays and radio waves.
- *Particle radiation* is generated through spontaneous delay of various

natural and artificial radioactive materials. Particles may also be generated by accelerating deuterons, electrons, cyclotrons and betatrons.

- *Ionizing radiation*: Radiation which carries enough energy to produce ionization in the materials by absorbing them, including living tissues.

General effects of radiation on tissues

- The cellular injury has been postulated to be due to a number of possible factors. They include:
 1. Toxic effects of protein breakdown products
 2. Inactivation of enzyme systems
 3. Coagulation or flocculation of protoplasmic colloids
 4. Denaturation of nucleoproteins
- In general, embryonic immature or poorly differentiated cells are more easily injured than differentiated cells of the same type.
- All cells show increased vulnerability to radiation injury at the time of mitotic division.
- Latent tissue injury is one of the most unusual phenomena related to X-ray or gamma radiation and it refers to *residual tissue damage*, thus the biological effects of radiation are cumulative, but show incomplete summation.

Radiosensitivity of normal cells and tissue

Table 11.1 describes the radiosensitivity of normal cells and tissues.

Table 11.1

Radiosensitivity of normal cells and tissues

Radiosensitive (2500 r or less kills or seriously injures many cells)	• Lymphocytes and lymphoblasts • Bone marrow (myeloblastic and erythroblastic cells) • Epithelium of intestine and stomach • Germ cells (ovary and testis)
Radioresponsive (2500–5000 r kills or seriously injures many cells)	• Epithelium of skin and skin appendages • Endothelium of blood vessels • Salivary glands • Bone and cartilage • Conjunctiva, cornea and lens of eye • Collagen and elastic tissue
Radioresistant (Over 5000 r kills or seriously injures many cells)	• Kidney • Liver • Thyroid • Pancreas • Pituitary • Adrenal and parathyroid glands • Mature bone and cartilage • Muscle • Brain and nervous tissue

Effect of radiation on oral and paraoral tissues

- Radiation effects are dependent upon a great number of factors such as source of radiation, total amount of radiation administered, the period of administration, the type of filtration used and total area of tissue irradiated.
- Bilateral parotitis, partial xerostomia and oral mucositis are commonly observed following irradiation.
- Bilateral parotitis will resolve spontaneously in 24–48 hours after irradiation.
- Saliva production during the first week after irradiation is noticeably reduced in amount and is thicker, ropier and more mucoid.
- The mucositis, which lasts 2–3 weeks, begins as swelling, soreness and whitening of oral mucosa.
- Within 48–72 hours, the lips, tongue and/or entire oral cavity show intense reddening of oral mucosa.
- Pain and denudation is also evident.
- After 2–3 weeks, there will be whitening of oral mucosa due to increased mitotic activity and prolonged retention of superficial epithelial cells leading to abnormally high degree of keratinization.
- Patients quickly lose their taste sensation due to the damage of microvilli and outer surface of the taste cells. However, it is transitory and taste acuity is restored within 60–120 days after completion of radiotherapy.

Treatment

- Palliation with warm salt water and sodium bicarbonate mouth rinses.
- Application of topical anaesthetics like lignocaine hydrochloride, oxethazaine, etc.

Effects on salivary glands

- Xerostomia or dryness of mouth is commonly present.
- Alteration in the salivary glands with decreased or even complete loss of saliva secretion may occur within 2 weeks.
- There is obvious damage to the acinar cells and decrease in the number of secretory granules.
- Congestion, oedema and inflammatory cell infiltration of the interstitial connective tissue are evident.
- Elevation of serum and urinary amylase is seen.
- No remarkable changes are seen in the ducts of salivary glands.

Effects on teeth

- Erupted teeth are also affected in patients with radiation therapy, but the damage is evident only after several years.
- The most common manifestation is peculiar destruction of tooth substance resembling dental caries and is referred as *radiation caries.* It often begins at the cervical areas of teeth. It resembles demineralization rather than true caries.
- Teeth become brittle and pieces of the enamel may fracture away from the tooth.
- Xerostomia of varying degrees favours the collection of debris on teeth and dental caries.
- Radiation of developing teeth in human beings causes disorganization of odontoblasts and formation of atypical dentine (ameloblasts are more resistant to radiation than odontoblasts), and sometimes complete cessation of odontogenesis resulting in anodontia or stunning of teeth.

Effects on bone

- Bone is relatively resistant to X-ray radiation although osteoblasts are sensitive.
- During intense or high dose irradiation, normal balance between the bone formation and bone resorption is disturbed, which results in localized

osteoporosis and decreased bone vitality.

- Irradiated bone does not react in the normal fashion to the infection due to damage of vascular bed with subsequent disturbance of typical inflammatory response.
- The healing response is delayed, poor and slow.
- Infection may spread to bone with little difficulty and spreads widely.

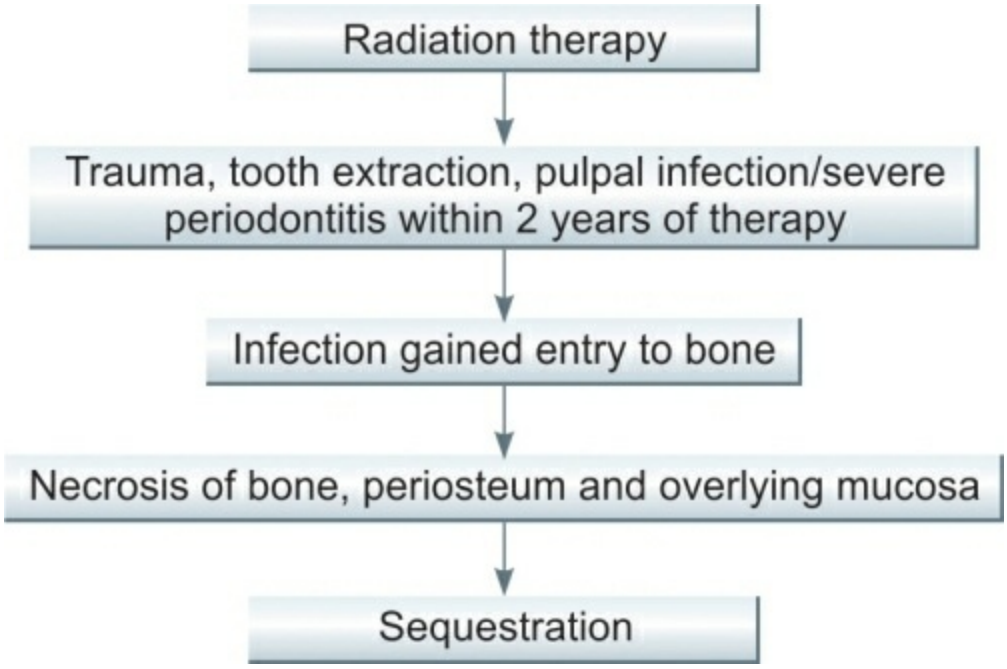
Osteoradionecrosis

Definition

It is an acute form of osteomyelitis caused by damage to the intraosseous blood vessels and is characterized by a chronic, painful infection and necrosis accompanied by late sequestration and sometimes permanent deformity.

Pathogenesis

- Mainly three factors are involved:
 1. Radiation
 2. Trauma
 3. Infection
- Predisposing factors leading to osteoradionecrosis are:
 - Irradiation of an area of previous surgery before adequate healing
 - Irradiation of lesions in close proximity to bone
 - High dose of irradiation with or without proper fractionation
 - Use of combination of external radiation and intraoral implants
 - Poor oral hygiene and continued use of irritants
 - Poor patient cooperation
 - Surgery in irradiated area
 - Indiscriminate use of prosthetic appliance
 - Failure to prevent trauma
 - Physical and nutritional problems
- Pathogenesis of osteoradionecrosis is illustrated in Flowchart 11.2.



FLOWCHART 11.2 Pathogenesis of osteoradionecrosis

Clinical features

- **Age.** Older age group.
- **Gender.** Male predilection.
- **Location.** Mandible is affected more frequently than the maxilla, due to differences in the blood supply between the two bones.
- **Signs and symptoms**
 - Intense pain, ulceration, swelling and sinuses formation with pus exudation are seen.
 - Severe foul smell, malocclusion and trismus are evident.
 - Sequestration of large fragments of necrotic bone occurs in the affected area.
 - Pathological fracture occurs frequently.

Radiographic features

Moth-eaten radiolucency is seen in the affected area of bone with the presence of opaque sequestra.

Histopathology (fig. 11.5)

- Bone with empty lacunae and devoid of osteoblastic rimming is commonly seen.

- The walls of regional blood vessels are thickened by fibrous connective tissue.
- Sometimes, endarteritis and periarteritis are also seen.
- The loose connective tissue, which replaces bone marrow, is infiltrated by microorganisms, lymphocytes, plasma cells and macrophages.
- The devitalized bone may undergo sequestration, although no clear line between vital and nonvital bone will be evident.
- The necrotic process may extend to involve complete irradiated bone.

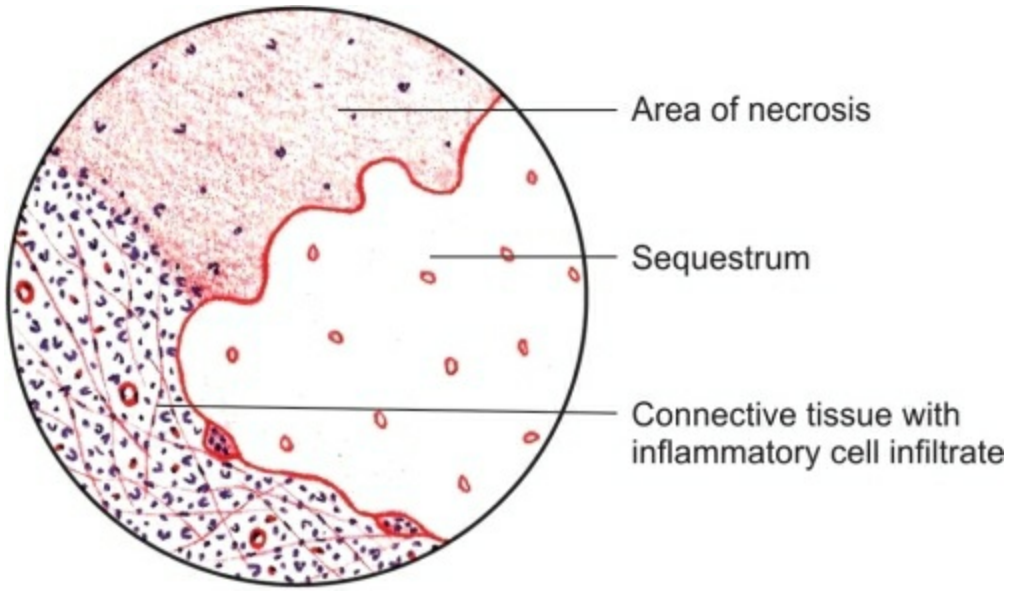


FIG. 11.5 Osteoradionecrosis.

Prognosis and predictive factors

- Debridement of necrotic tissues should be done along with removal of the sequestrum.
- Administration of intravenous antibiotics and hyperbaric oxygen therapy.
- Maintenance of good oral hygiene.
- Minor or major surgeries should be avoided at least for 2 years following radiotherapy.

Chemical injuries of oral cavity

- Oral cavity frequently manifests a serious reaction to wide variety of drugs and chemicals.

- Tissue reaction may be due to local response to a severe irritant or due to administration of systemic drugs.

Drugs and chemicals used locally in dentistry

The materials used locally which induce a nonallergic reaction are chiefly irritants or caustics, many of which are used by the dentist in various therapeutic or technical problems.

Aspirin (acetylsalicylic acid)

- Aspirin tablets are used mistakenly by many people as a local obtundent, especially for the relief of toothache.
- It is also available in powder form.
- Initially, burning sensation of the oral mucosa is seen.
- Surface appears blanched and whitened in appearance.
- Separation and sloughing of the epithelium with frequent bleeding is seen.
- Pain is evident.
- Healing takes place usually within 1 or 2 weeks.

Endodontic materials

- Some endodontic materials cause soft tissue damage resulting in deep spread of inflammation and necrosis.
- Paraformaldehyde is commonly used to devitalize the inflamed pulp. It may leak from the pulp chamber into the surrounding tissue and causes necrosis of the gingiva and bone.

Sodium hypochlorite

- Commonly used as a root canal irrigant.
- Although it is considered safe, it may cause severe tissue damage, if it comes in contact with tissue or extrudes beyond apex.
- It also causes haemolysis and ulceration.
- Microscopically, it causes damage to endothelial cells and fibroblasts, and inhibits neutrophil migration.

Hydrogen peroxide

- It is a caustic agent.
- Upon contact with mucosa, it causes burning sensation and releases toxic-

free radicals, perhydroxyl anion or both.
- It is thermodynamically unstable and may explode, if not refrigerated or stored in dark container.
- 30–35% hydrogen peroxide (superoxal) is used along with heat (thermocatalytic) for bleaching teeth.
- This thermocatalytic process damages the tooth by causing irritation to cementum and periodontal ligament leading to cervical root resorption.

Phenol

- It is used as a cavity sterilizing agent as well as cauterizing agent.
- It can be used for treating aphthous ulcers.
- Extensive mucosal necrosis and underlying bone loss are seen below medication (0.5%), when used topically.

Silver nitrate

- It is used in dentistry as a cavity sterilizing material, caries preventive and chemical cautery agent.
- Previously, it was a popular medicament for aphthous ulcerations, because the chemical cautery used to bring about rapid pain relief by destroying the nerve endings.
- Overzealous usage produces severe painful burns of the oral mucosa.

Drugs and chemicals used systemically in dentistry

The systemic administration of various drugs and chemicals evokes an oral reaction which is not due to an allergy or sensitivity; instead this reaction will be a part of generalized epidermal reaction.

Lead

Aetiology

- Lead poisoning *(plumbism)* occurs chiefly as an occupational hazard.
- In adults, it is mainly due to inhalation of lead vapour or dust.
- In infants, it is due to chewing wood or toys with lead-containing paint.

Clinical features

- Gastrointestinal disturbances, which include nausea, vomiting, colic and constipation.
- Peripheral neuritis may produce characteristic wrist-drop or foot-drop.

- Encephalitis may also occur.
- Blood changes are also seen, e.g. hypochromic anaemia with basophilic stippling of red blood cells.
- Skeletal changes due to deposition of lead in growing bone occur among children.

Oral manifestations

- *Lead line (Burton's line),* a grey or bluish black line of sulphide pigmentation occurs in the gingiva (marginal) resulting from the action of bacterial hydrogen sulphide on lead in the gingival sulcus to produce lead sulphide precipitate. It is more diffuse compared to *bismuth line.* Sometimes, it may also be found in buccal mucosa and tongue.
- Ulcerative stomatitis is seen.
- Tremor of the tongue on thrusting is evident.
- Excessive salivation and metallic taste are commonly present.

Treatment

- Oral lesions are treated secondary to systemic treatment.
- Prognosis depends upon the systemic condition of the patient.

Mercury

Aetiology

Mercury poisoning (mercurialism) occurs mainly due to the occupational hazard or therapeutic use of this compound.

Clinical features

- Elemental mercury is poorly absorbed and its ingestion is harmless.
- Inhalation of mercury vapours is very hazardous with a high rate of absorption and systemic retention.
- Ingestion of mercury salts, e.g. mercurous chloride is also associated with adverse reactions.
- It may be in acute or in chronic form.
- Systemic reactions in the acute form are so serious that the oral manifestations need not be considered.
- Acute exposure—abdominal pain, vomiting, diarrhoea, thirst, nephritis, pharyngitis and gingivitis.
- Chronic mercurialism occurs after prolonged contact with mercury

compound, or secondary to liquid mercury spills.
- Chronic exposure—gastric disturbances, diarrhoea, excitability, insomnia, headache and mental depression are commonly seen. Fine tremors of fingers and limbs as well as lips and tongue are also seen.
- Chronic mercury exposure in infants and children causes *acrodynia (pink disease or swift disease).*

Oral manifestations

- Increased flow of saliva (ptyalism).
- Metallic taste in the mouth due to excretion of mercury in saliva.
- Tongue and salivary glands are swollen, enlarged and painful.
- Ulcerations on the gingiva, palate and tongue are common.
- Occasionally, hyperaemia and swelling of gingiva are seen.
- Pigmentation line on the gingiva, similar to bismuth and lead line, may occur as a result of dark sulphide compound deposition.
- Loosening of teeth even leading to exfoliation of teeth is reported.

Treatment

- Treatment is supportive and secondary to mercury poisoning.
- Prognosis is usually good.

Acrodynia

(Synonyms: Pink disease; swift disease)

It is an uncommon disease caused due to chronic mercury exposure in infants and children.

Aetiology

- Unknown.
- The source of mercury may be teething powder, ammoniated mercury ointment and calomel lotion.

Clinical features

- It occurs more frequently in young infants before the age of 2 years.
- The cold clammy skin of hands, feet, nose, ears and cheeks becomes erythematous.
- Maculopapular rashes which are extremely pruritic are seen.
- Severe sweating is evident.
- Extreme irritability, photophobia with increased lacrimation, muscular

weakness, tachycardia, hypertension, insomnia, gastrointestinal upset and stomatitis are seen.

Oral manifestations

- Profuse salivation and often dribbling are evident.
- Gingiva becomes extremely sensitive, painful and shows ulceration.
- Bruxism, loosening and premature shedding of teeth are seen.

Treatment

- Remove the source of mercury.
- Immediate chelation therapy.
- Administration of dimercaprol, D-penicillamine and DMSA (2,3-dimercapto-1-propanesulfonic acid) has prone successful.

Silver

(Synonyms: Argyria; argyrosis)
Silver is commonly a medicament due to its antibacterial properties.

Aetiology

- Chronic exposure to silver compounds may occur as a result of occupational or therapeutic use.
- Silver compounds are used topically in nasal drops and systemically for a variety of disorders including mental illness, epilepsy, nicotine addiction, common cold, sinusitis, syphilis and gonorrhoea.

Clinical features

- Acute silver intoxication—coma, pleural oedema, haemolysis and bone marrow failure.
- Chronic systemic silver intoxication—*argyria*.
- Subepithelial deposition of silver in the skin and mucous membrane results in diffuse greyish discolouration.
- Sclera and nails are also pigmented.
- Slate blue silver line occurs along the gingival margins due to secondary deposition of metallic silver and silver sulphide pigments.
- Oral mucous membrane often exhibits diffuse blue-black discolouration.

Amalgam tattoo

Amalgam tattoo of oral mucous membrane is a common finding occurring due to following reasons:

- Condensation in gingiva during amalgam restoration.
- Particles enter mucosa through lacerations, which occurs usually during removal of old amalgam restorations.
- Broken pieces may introduce into socket during tooth extraction.
- Particles enter surgical wound during root canal treatment with retrograde amalgam restoration.

Clinical features

- It appears as macules or as a slightly raised blue, black or grey lesion.
- It usually occurs in gingiva, buccal mucosa and alveolar mucosa.
- It is frequently mistaken for melanin pigmentation lesions.

Histopathology

- Usually, it does not show any tissue reaction or inflammatory response.
- In few cases, chronic inflammatory reaction manifesting as a foreign body granuloma with either foreign body–type giant cells or Langhans–type giant cells.
- The amalgam fragments appear as black or olive-brown granules, which are commonly arranged in linear fashion along collagen fibres and around blood vessels.
- In addition, they are also found along nerve sheaths, striated muscle fibres and along the basement membrane of mucosal epithelium.

Bismuth

- Bismuth was used widely in the past for the treatment of venereal diseases and various dermatoses.
- Bismuth iodoform pastes are still used by otolaryngologists and oral surgeons as surgical packs.

Clinical features

- Bismuth pigmentation of the oral mucosa is seen particularly in the gingiva and buccal mucosa.
- *Bismuth line*, a thin black-blue line in the marginal gingiva which is sometimes confined to the gingival papilla only.
- Pigmentation may be seen in buccal mucosa, lips, ventral surface of the tongue, around partially erupted third molars or around the periphery of

an ulcer as an anachoretic phenomenon.

- These pigmentations represent precipitated granules of bismuth sulphide produced by the action of hydrogen sulphide.
- Hydrogen sulphide is formed through bacterial degradation of organic material or food debris.
- Pigmentation will be irritating locally but not destructive as mercuric sulphide.
- Ptyalism, burning sensation of the mucosa, stomatitis, metallic taste and ulcerations are also seen.
- Lingual alterations like black hairy tongue and elongated papillae are seen.

Histopathology

- The granules of sulphide are seen in the tissue section as small, irregular black collections of pigments.
- Sometimes, pigmented granules are present more in the perivascular location, but other times seen diffuse without apparent arrangement.
- Rarely, these sulphide granules are also seen in endothelial cells or in mononuclear phagocytes in the tissue.
- It provokes no foreign body response and may be present even in the absence of inflammation.

Treatment

- No specific treatment.
- Bleaching with hydrogen peroxide.
- Eventually, the pigmentation disappears, if the bismuth use is discontinued.
- The prognosis of the condition is very good.

Arsenic

Arsenic compounds are usually prescribed for asthma and skin disorders such as psoriasis.

Aetiology

It is often caused as an occupational hazard because of the wide use of this metal in industry.

Clinical features

- Both organic and inorganic forms may produce symptoms of acute and chronic poisoning.
- Diffuse macular hyperpigmentation and increased melanin production is evident.
- Palmar and plantar hyperkeratosis and numerous premalignant skin lesions called *arsenical keratoses* are seen.
- Development of basal cell carcinoma and cutaneous squamous cell carcinoma has been seen after years of exposure.

Oral manifestations

- Ptyalism, painful areas of necrotizing ulcerative stomatitis and extensive dorsal hyperkeratosis of tongue are seen.
- Inflammation of oral mucous membrane and severe gingivitis are evident.

Tetracycline

- Discolouration of either deciduous or permanent teeth may occur as a result of tetracycline deposition during prophylactic or therapeutic regimens instituted either in the pregnant female or postpartum in the infant.
- Tetracycline and its homologues have an affinity for deposition in bone and tooth substance through the formation of complex with calcium ions in the surface of the microcrystals of hydroxyapatite.
- The severity is determined by stage of tooth development during the time of drug administration.
- Since tetracycline does cross the placental barrier, it may involve those deciduous teeth which develop during antepartum, although the discolouration depends upon dosage, length of time of administration and the form of tetracycline.
- The use of oxytetracycline or doxycycline may diminish teeth discolouration, whereas minocycline hydrochloride, a semisynthetic derivative of tetracycline, causes discolouration due to binding with certain type of collagenous tissues like dentine, dental pulp, bone and dermis.

Clinical features

- Affected teeth have yellowish or brownish-grey discolouration, which is more pronounced at the time of teeth eruption. This discolouration gradually becomes more brownish after exposure to light.

- Tetracycline fluoresces under ultraviolet light with bright yellow colour. However, this fluorescence gradually diminishes with time.
- Dentine is more heavily stained than the enamel.
- Minocycline hydrochloride causes discolouration of skin, nails, conjunctiva, bone and teeth.
- Palate or anterior alveolar mucosa has a distinctive blue-grey appearance due to underlying black bone appears through the thin translucent mucosa.
- The incisal edge of the fully erupted teeth shows blue-grey discolouration, middle one-third minimally involved and exposed roots reveal dark green discolouration.

Bisphosphonate

- It is a potent antiresorptive agent used in the management of benign and malignant diseases such as multiple myeloma and metastatic bone diseases.
- It acts by blocking the dissolution of hydroxyapatite crystals, inhibiting differentiation of bone marrow precursors into osteoclasts and inhibiting the osteoclasts function.
- It causes osteonecrosis of the jaws resulting from the inability of hypodynamic and hypovascular bone to meet an increased demand for repair and remodelling.
- Dental extraction has been identified as a predisposing factor for osteonecrosis of alveolar bone.

Treatment

- Responds well to surgical intervention, antibiotic therapy, hyperbaric oxygen therapy and topical use of mouth rinses.
- Sequential removal of sequestrum with minimal epithelial manipulation is recommended.

Dilantin sodium (sodium diphenylhydantoinate)/cyclosporin/nifedipine

It is discussed in Chapter 7 *Diseases of the Periodontium* under *'Gingival Enlargements'*.

Key points

- *Pulpal changes* during high speed instruments cavity preparation—changes in ground substance, oedema, fibrosis, odontoblastic disruption and reduced predentine formation.
- *Bruxism* is the habitual grinding or clenching of the teeth either during sleep or as an unconscious habit during waking hours.
- *Subluxation* refers to abnormal loosening of the tooth without displacement due to sudden trauma.
- *Avulsion* is dislocation of the tooth from its socket due to traumatic injury.
- *Ankylosis* refers to union of two adjacent hard structures. Fusion between the tooth and the bone is termed as *tooth ankylosis.*
- *Simple fracture:* The bone is broken completely and the overlying structures are intact and are not exposed to exterior.
- *Greenstick fracture:* Common in soft bones of infants and children, which bends when partially broken.
- *Compound fracture:* External wound is associated with the break.
- *Comminuted fracture:* Bone is crushed or splinted and it may be exposed to exterior.
- *Osteoradionecrosis* is an acute form of osteomyelitis caused due to irradiation damage to the intraosseous blood vessels and is characterized by a chronic, painful infection and necrosis accompanied by sequestration.
- *Lead poisoning (plumbism):* Lead line (Burton's line), ulcerative stomatitis, tremor of the tongue, excessive salivation and metallic taste.
- *Mercury poisoning (mercurialism):* Acrodynia, ptyalism, metallic taste, tongue and salivary glands are enlarged and painful, ulceration on gingiva, palate and tongue, pigmentation line on the gingiva and loosening of teeth.
- *Silver poisoning (argyria, argyrosis):* Pigmentation of the skin, mucous membrane, sclera and nails, and blue silver line along the gingival margins.
- *Bismuth poisoning:* Bismuth line, pigmentation of buccal mucosa, lips, tongue, ptyalism, burning sensation of the mucosa, stomatitis, metallic taste and ulcerations.
- *Arsenic poisoning:* Ptyalism, necrotizing ulcerative stomatitis, hyperkeratosis of tongue, mucositis and severe gingivitis.
- *Tetracycline* causes discolouration of deciduous or permanent teeth, blue-grey appearance of palate or anterior alveolar mucosa.

Frequently asked questions

1. Discuss the physical injuries affecting the dental hard tissues.
2. Discuss the effect of various restorative materials on dental tissues.
3. Bruxism.
4. Discuss the injuries associated with supporting structures of the tooth.
5. Traumatic Ulcerative Granuloma with Stromal Eosinophilia (TUGSE).
6. Epulis fissuratum.
7. Discuss the effect of radiation on oral tissues.
8. Osteoradionecrosis.
9. Argyria.
10. Acrodynia/*Pink disease*/*Swift disease*.

CHAPTER 12

Regressive alterations of the teeth

Regressive changes in the dental tissues include variety of alterations that are not necessarily related either aetiologically or pathogenetically. Some of these changes are associated with the general ageing process of the individual.

Attrition (fig. 12.1a)

Definition

- It is defined as the physiologic wearing of tooth as a result of tooth-to-tooth contact as in mastication.
- This phenomenon is physiological rather than pathological, and is associated with the ageing process.

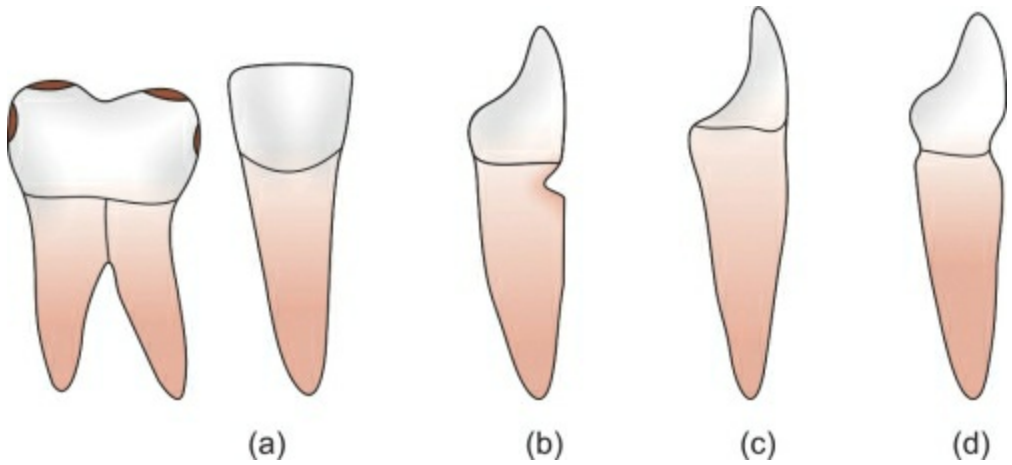


FIG. 12.1 (a) Attrition; (b) abrasion; (c) erosion; (d) abfraction.

Aetiology

- Ageing of the individual
- Habits such as chewing tobacco or gum
- Developmental abnormalities causing traumatic occlusion
- Psychological disorder patients
- Coarseness of diet
- Bruxism

Clinical features

- **Age.** Any age.
- **Gender.** Men exhibit severe attrition compared to women of comparable age.
- **Location**
 - It occurs on the occlusal, incisal and proximal surfaces of the teeth.
 - It is seen in both deciduous and permanent dentitions.
- **Signs and symptoms**
 - The first clinical manifestation may be the appearance of a small polished facet on a cusp tip or ridge or a slight flattening of an incisal edge.
 - Due to physiological mobility of the teeth, similar facets may also occur at the contact points on the proximal surfaces of the teeth.
 - As the person becomes older, the wear continues and there is a gradual reduction in the cusp height and flattening of the occlusal planes.
 - In severe conditions, teeth may be worn down nearly to the gingiva.
 - Exposure of dentinal tubules and subsequent irritation of odontoblastic process result in the formation of secondary dentine pulpal to the primary dentine and this serves as an aid to protect the pulp from further injury.

Treatment

- Identification and correction of aetiological agents like parafunctional chewing habits, developmental abnormalities, etc.
- Construction of occlusal guard.
- In severe cases, tooth can be protected by metallic or ceramic crowns.

Abrasion (fig. 12.1b)

Abrasion is the pathological wearing of tooth substance due to some abnormal mechanical processes.

Aetiology

- Dentifrices and tooth brush can cause remarkable wear of cementum and dentine, when these are used injudiciously in horizontal rather than vertical direction.
- Abrasion is related to habits or occupation of the individuals. Incisal notching is commonly seen among carpenters, pipe smokers,

shoemakers, tailors, etc.
- The improper use of dental floss and tooth picks can also cause abrasion.

Clinical features

- **Age.** Any age.
- **Gender.** No sex predilection.
- **Location**
 - Right-hand tooth brushing individuals—buccal surfaces of left posterior teeth.
 - Left-hand tooth brushing individuals—buccal surfaces of right posterior teeth.
- **Signs and symptoms**
 - Abrasion manifests as a V-shaped or wedge-shaped ditch on the root side of the cementoenamel junction with some gingival recession.
 - Abrasion usually occurs on the exposed root surfaces of the teeth, but it can also be seen on incisal or proximal surfaces.
 - The habitual opening of bobby pins with the teeth may result in a notching of the incisal edge of maxillary central incisors.
 - In pipe smokers, abrasions develop on the incisal surfaces of upper and lower anterior teeth. The lesion is characterized by a well-polished notch, whose shape typically matches with the shape of the pipe stem used for smoking.
 - The exposure of dentinal tubules and irritation of the odontoblastic process stimulate the formation of secondary dentine and this serves as an aid to protect the tooth against pulp exposure.

Treatment

- Educate the patient about correct method of tooth brushing.
- Restoration helps to keep the tooth surface intact and also prevents further tooth wear.

Erosion (fig. 12.1c)

Erosion is defined as irreversible loss of dental hard tissue by a chemical process that does not involve bacteria.

Aetiology

- In erosion, dissolution of the mineralized tooth structure occurs upon

contacts with acids, which are introduced in the oral cavity either from extrinsic sources or intrinsic sources.

- Extrinsic causes are mainly the acidic beverages and citrus fruits.
- Intrinsic causes include gastroesophageal reflux and vomiting.

Extrinsic causes

- It is mainly due to contact with acidic media like food stuff or by iatrogenic exposure.
- Extrinsic causes (source outside the body) include acidic beverages and foods, dietary acids, medications, environmental acids, carbonated drinks, sports drinks, fruits and fruit juices.
- It is also seen among professional swimmers, who work regularly in swimming pools and occupational wine tasters.

Intrinsic causes

- Intrinsic causes (acid source inside the body) for erosion of teeth are gastric acids (pH < 1), which are regurgitated into oesophagus and mouth due to gastroesophageal reflux or excessive vomiting.
- Gastroesophageal reflux syndrome (GERD) is a common condition affecting adult population and one of the causes for the dental erosion. In this condition, gastric contents pass involuntarily into oesophagus and can escape into the mouth. This is caused by increased abdominal pressure, inappropriate relaxation of the lower oesophageal sphincter or increased acid production by the stomach.
- Chronic excessive vomiting, eating disorder such as anorexia bulimia is also recognized in causing erosion of the teeth on palatal aspect of maxillary anterior teeth.

Clinical features

- **Age.** Any age.
- **Gender.** No sex predilection.
- **Location**
 - Extrinsic causes: Labial or buccal surfaces of teeth
 - Intrinsic causes: Lingual or palatal surfaces of teeth
- **Signs and symptoms**
 - Usually, it manifests as shallow, broad, scooped-out concavities within the smooth surface enamel.
 - Sometimes, cupping of occlusal surfaces (incisal grooving) with dentine

exposure is seen. It also involves proximal surfaces of teeth.

- Erosion from dental exposure to gastric secretions is termed *perimolysis.*
- Raised amalgam restorations above the level of the tooth surface are seen.
- Hypersensitivity of teeth is evident due to loss of enamel and it may also trigger the secondary dentine formation.

Saliva as a modifying factor for erosion

- The salivary buffering capacity maintains the normal pH of oral cavity by neutralizing extrinsic and intrinsic acids, which in turn prevents erosion of teeth.
- Moreover, mineral ions in saliva can cause remineralization of the damaged enamel by the acids.
- There is a relationship between the salivary flow rate and its buffering capacity (buffering capacity of saliva increases as the flow rate increases). Therefore, if the salivary flow rate is decreased either due to medications or disease, there will be more erosion of teeth.
- Increase in the citric acid and mucin content in saliva prevents the precipitation of mineral ions from saliva and hampers the remineralization process.

Treatment

- Identification of the aetiology is the first step in management of erosion.
- GERD cases should be referred to a general physician for complete evaluation and therapy is indicated.
- Patients with salivary hypofunction may benefit with the use of sugarless chewing gum to increase the residual salivary flow.

Abfraction (fig. 12.1d)

Abfraction is the pathological loss of tooth structure from occlusal stress that creates repeated tooth flexure with failure of enamel and dentine at a location away from the point of loading.

Aetiology

- Static forces: Forces produced during swallowing, tongue thrusting and clenching of teeth.
- Cyclic forces: Forces produced during chewing.

- Individuals with open bite or deep class I cavity are more prone to develop abfraction of tooth.
- The breakdown of tooth structures is dependent on the magnitude, duration, direction, frequency and location of the forces.

Clinical features

- **Age.** Any age.
- **Gender.** No sex predilection.
- **Location**
 - Labial or buccal surface of teeth is involved.
 - Usually gingival third of the clinical crown is affected.
- **Signs and symptoms**
 - Dentine is able to withstand greater tensile stress than enamel.
 - When occlusal forces are applied eccentrically on a tooth, the tensile stress is concentrated at the cervical fulcrum, leading to flexure that may produce disruption in the chemical bonds of the enamel crystals in the cervical areas. Once damaged, the cracked enamel is lost or more easily removed by erosion or abrasion.
 - Sensitivity of tooth, sign of traumatic occlusion and wearing on occlusal surface are often seen.
 - Repeated failure of restorations on the cervical area due to damaging lateral forces.

Treatment

- Identification and correction of aetiological agent.
- Restoration helps to keep the tooth surface intact and prevents further tooth wear.

Dental sclerosis

(Synonym: Transparent dentine)

- Sclerosis of primary dentine is a regressive alteration in tooth characterized by calcification of the dentinal tubules.
- It occurs as a result of injury to the dentine, dental caries, attrition, abrasion, erosion or due to normal ageing process.
- The exact mechanism of dentinal sclerosis is not clear, although the most likely source of calcium salts is the fluid or dental lymph within the tubules.

- In ground sections, it is readily recognized due to the difference between the refractive indices of the sclerotic dentinal tubules and the adjacent normal tubules.
- It appears dark in reflected light and transparent in transmitted light.
- The increased mineralization of the tooth decreases the conductivity of the odontoblastic process and also slows an advancing carious process.

Dead tracts

- Dead tracts in dentine are seen in ground sections of teeth and are manifested as a black zone in transmitted light and as a white zone in reflected light.
- This optical phenomenon is due to differences in the refractive indices of the affected tubules and normal tubules.
- The nature of the change in the affected tubules is not known, although these tubules are not calcified and are permeable to the penetration of dyes.
- Dead tracts are most commonly observed in the area of narrow pulpal horns because of crowding of odontoblasts.
- These are a group of dead, degenerated odontoblastic processes in the dentinal tubules. These tubules are empty and get filled with air; therefore these appear dark in transmitted light. Sometimes, dentinal tubules may be filled with fluid or gaseous substance.

Secondary dentine

- Secondary dentine is formed and deposited in response to a normal or slightly abnormal stimulus after the complete formation of tooth.
- The dentinal tubules are irregularly arranged in secondary dentine. It contains less calcium, phosphorus and collagenous matrix.
- There are generally two types of secondary dentine:
 1. Physiological secondary dentine
 2. Reparative secondary dentine

Physiological secondary dentine

- It is formed after the root completion and eruption of teeth.
- It is a regular, uniform layer of dentine around the pulp chamber that is laid down throughout the life of the tooth.

- It is formed as a result of physiological ageing process and is produced more slowly than primary dentine.

Reparative secondary dentine

(Synonyms: Tertiary dentine; reactive dentine)

- It is the dentine that forms around the pulp chamber as a result of irritation, attrition, abrasion, erosion or operative procedures.
- Any of these processes results in the degeneration of a large number of odontoblasts. However, few odontoblasts survive and keep forming dentine. The degenerated cells are replaced by the movement of undifferentiated cells from the cell-rich zone or from the undifferentiated perivascular cells present in the deeper portion of the pulp. The reparative dentine is formed by the remaining as well as the newly differentiated odontoblasts.
- The quality and quantity of tertiary dentine is related to the intensity and duration of the stimulus.

Clinical features

- No significant clinical features are present to determine secondary dentine formation.
- There is an evident decrease in tooth sensitivity, when secondary dentine formation is extensive in elderly individuals.
- This type of dentine forms an additional insulating layer in tooth, thus the eventual pulp involvement is usually delayed.

Radiographic features

- Radiopaque material is noted particularly in the pulp horn area as well as on the proximal walls of teeth with proximal caries.
- Decrease in the size of the pulp chamber and root canals are evident.

Histopathology (fig. 12.2)

- Usually, secondary dentine exhibits few irregular dentinal tubules with tortuous course—*tubular dentine*.
- A bend is seen in the dentinal tubules at the junction of primary and secondary dentines.
- In decalcified stained sections, primary dentine is well demarcated from the secondary dentine by a deeply stained line.

- Occasionally, secondary dentine is formed at a rapid rate and odontoblasts may become entrapped resembling bone. This calcified tissue is termed as *osteodentine.*
- Sometimes, *irregular dentine* (dentine containing irregularly arranged dentinal tubules) or *mixed dentine* (combination of osteodentine, irregular and tubular dentine) is seen.

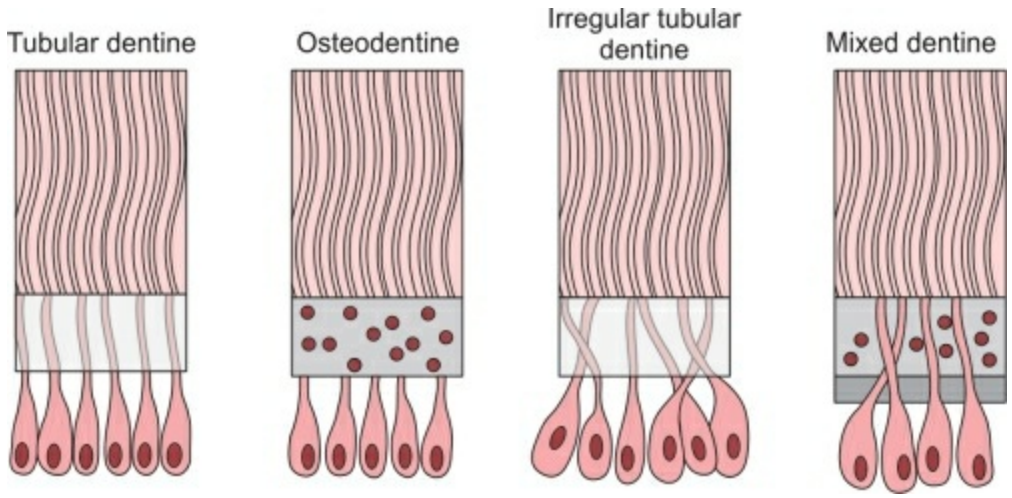


FIG. 12.2 Tertiary dentine

Pulp calcification

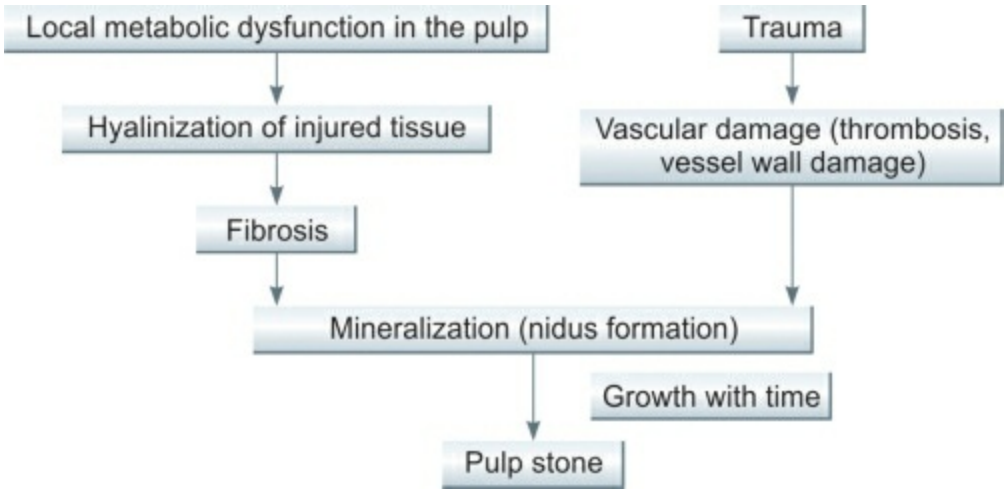
Deposition of calcified mass(es) within the dental pulp for no apparent reasons is called *pulp calcification.*

Aetiology

- Unknown.
- It may be age-related process.
- Local pathological changes like trauma, dental caries, etc in the dental pulp.
- It is also seen in various conditions like dentinogenesis imperfecta, dentine dysplasia, Ehlers–Danlos syndrome and regional odontodysplasia.

Pathogenesis

Flowchart 12.1 depicts the pathogenesis of pulp calcification.



FLOWCHART 12.1 Pathogenesis of pulp calcification

Classification

Pulp calcification may be:

- Denticles
- Pulp stones (pulp nodules)
- Diffuse calcification

Denticles

- Denticles are small masses of tubular dentine formed within the pulp near the furcation area of tooth.
- These are believed to form as a result of epithelio-mesenchymal interaction within the developing pulp. Epithelial strands originating from the root sheath or cervical extensions into the pulp chamber adjacent to furcations induce odontoblastic differentiation of the surrounding mesenchyme of the dental papilla, forming the core of the denticles. These odontoblasts produce tubular dentine as they move away from the central core of epithelium.
- Since denticle development typically precedes completion of the primary dentine, most of the denticles become attached to or embedded in the dentine.

Pulp stones

Pulp stones can be of two types:

1. True pulp stones
2. False pulp stones

True pulp stones

- They are made up of localized masses of calcified tissue that resemble dentine because of the tubular structure.
- These nodules greatly resemble secondary dentine than primary dentine.
- These are more common in pulp chamber than in root canals.
- These can be subdivided based on their attachment to the wall of pulp chamber:
 - *Free pulp stones:* These pulp stones lay entirely within the pulp tissue and are not attached to dentinal walls.
 - *Attached pulp stones*: These pulp stones are attached to the dentinal walls. These may be partial or completely embedded in the dentinal walls. Attached pulp stones are more common than the true type.
 - *Interstitial (embedded) pulp stones*: These pulp stones are surrounded by reactionary or secondary dentine.

False pulp stones

- These are composed of localized masses of calcified materials and unlike true denticles do not exhibit any dentinal tubules.
- The nodular masses are made up of concentric layers or lamellae deposited around a central nidus. The exact nature of this nidus is unknown. Johnson and Bevelander believe that these are composed of cells, as yet unidentified, around which a layer of reticular fibres is laid down that subsequently calcify.
- False pulp stones can be *free* or *attached or interstitial (embedded) pulp stones.*
- As the concentric deposition of calcified material continues, it approximates and finally is in apposition with the dentinal wall. It may be eventually surrounded by secondary dentine and is then referred to as *interstitial (embedded) pulp stone.*
- These are most commonly seen in pulp chamber than in the root canals and are larger than true pulp stones.

Diffuse calcification

It is most commonly seen in root canals of the teeth and resembles the calcification seen in other tissue of the body following degeneration. This type of calcification is frequently termed *calcific degeneration.*

Radiographic features

- Denticles and pulp stones can reach sufficient size to be detected on intraoral radiographs as radiopaque enlargements within the pulp chamber or canal.
- Diffuse calcifications are not detectable radiographically.

Histopathology (fig. 12.3)

- Denticles consist of tubular dentine surrounding a central nest of epithelium. With time, the central epithelium degenerates and the tubules undergo sclerosis.
- True pulp stones are localized masses of tubular dentine, which may be free, attached or embedded type of calcifications.
- False pulp stones are nodular masses made up of central amorphous mass of irregular calcification surrounded by concentric lamellar rings of regular calcified material.
- Pulp stones can be free, attached or embedded type of calcifications, depending upon their attachment to the wall of pulp chamber.
- Diffuse calcifications are composed of fine fibrillar and irregular calcifications that develop in the pulp chambers and canals. This material is often deposited in a linear fashion along the course of a blood vessel or nerves.

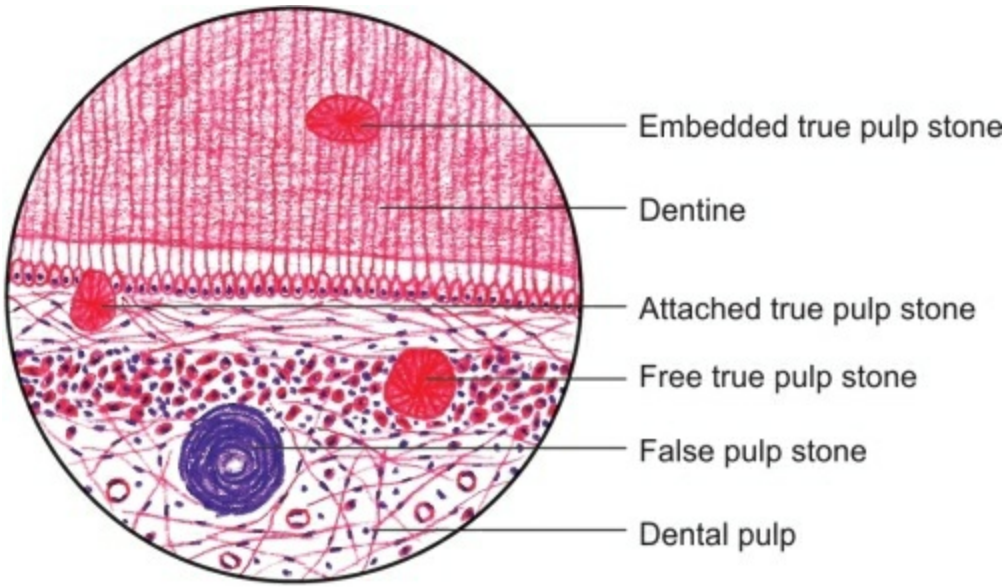


FIG. 12.3 Pulp stones.

Resorption of teeth

Definition

Tooth resorption is defined as a chronic progressive damage or loss of tooth structures due to the action of some specialized cells known as *odontoclasts*.

- Resorption of teeth occurs as a physiological phenomenon as in case of deciduous teeth root resorption.
- The roots of permanent teeth may undergo resorption in response to a variety of stimuli.
- It may begin either on the external surface (external resorption) or inside the tooth (internal resorption) on the pulpal surface.
- The chief causes or stimulations causing resorption include:
 - External resorption
 - Periapical inflammation
 - Reimplantation of teeth
 - Tumours and cysts
 - Excessive mechanical and occlusal forces
 - Impaction of teeth
 - Idiopathic
 - Internal resorption: Idiopathic

External resorption

Periapical inflammation

- Resorption of calcified tissue occurs in the same manner as that of bone.
- Presence of osteoclasts is an important feature in the areas of active resorption.
- Periapical granuloma arising as a result of pulpal infection or trauma causes resorption of root apex, if the inflammatory lesion persists for a sufficient period of time.
- Bone resorption occurs more readily in highly vascular areas than in avascular areas.
- In dental radiographs, it appears as a slight raggedness or blunting of the root apex in the early stages which may proceed to a severe loss of tooth substance.

Reimplantation of teeth

- The reimplantation or transplantation of teeth results in severe resorption of the roots.
- The involved tooth regardless of root canal treated or filled, it is considered to be nonvital.
- Usually, tooth root will be resorbed and replaced by bone, which produces ankylosis.
- If the tooth root does not resorb completely, the ensuing ankylosis may result in a functional tooth.
- Many reimplanted teeth exhibit complete resorption of root and may result in exfoliation of tooth.

Tumours and cyst

- Resorption of roots by tumours and cysts is mainly due to pressure phenomenon.
- Benign tumours and cysts are more likely to produce displacement rather than actual destruction of tooth as in case of malignant tumours.
- An apical periodontal cyst arising as a result of pulp infection may exert pressure on the apex of the involved or adjacent tooth, which stimulates the connective tissues to form osteoclasts and resorption.

Excessive mechanical or occlusal forces

- Usually, an excessive mechanical force which causes root resorption is associated with orthodontic treatment.
- Individuals with orthodontic treatment frequently exhibit multiple areas of root resorption, irrespective of type of appliance, duration and degree of force exerted. (Effect of orthodontic tooth movement is discussed in Chapter 11 Physical and Chemical Injuries of the Oral Cavity.)

Impacted teeth

- Teeth that are completely impacted or embedded in bone will undergo resorption of the crown or both crown and root.
- Resorption occurs most commonly among teeth of the maxillary arch.
- Although maxillary and mandibular third molars are commonly impacted, cuspids undergo resorption more frequently than third molars.
- Impacted supernumerary teeth, particularly mesiodens, are also more prone to undergo resorption.
- Impacted teeth may also cause resorption of the roots of adjacent teeth

without being resorbed themselves. This is particularly common among horizontally or mesioangularly impacted mandibular third molar impinging on the roots of second molar. The interposed connective tissue between the second and third molars is activated due to the pressure of third molar, which in turn forms the resorptive cells and sets the stage for tooth destruction.

Idiopathic resorption

- Roots of permanent teeth may undergo certain amount of resorption in apparently normal adults without any obvious aetiology.
- Systemic disorders like endocrine disturbances and genetic factors may be involved.
- Idiopathic resorption of teeth is commonly seen among females compared to males.
- Maxillary bicuspids, maxillary and mandibular central incisors are commonly involved.
- Sometimes, multiple teeth idiopathic root resorption may be seen, involving all or nearly all of the teeth.

Internal resorption

(Synonyms: Pink tooth of Mummery; odontoclastoma; internal granuloma)

Definition

Internal resorption is an unusual form of tooth resorption that begins centrally within the tooth, apparently initiated, in most cases, by a peculiar inflammatory hyperplasia of the pulp.

Aetiology

- Unknown.
- It may be inflammatory response to pulpal injury.
- Initiating factors may be trauma, dental caries, etc.
- The inflammatory reaction in the pulp causes activation of osteoclasts or odontoclasts in the internal surfaces of the root or crown, which result in the resorption of dentine.
- Some authors suggest that the true internal resorption does not exist but rather is a result of resorption of the tooth and invasion of the pulp by granulation tissue arising in the periodontium.

Clinical features

- **Age.** Younger age group.
- **Gender.** Female predilection is seen.
- **Location**
 - Both maxillary and mandibular arches are equally involved.
 - It may involve single tooth or even sometimes multiple teeth.
 - It may involve any tooth—incisors, cuspids, bicuspids and molars.
 - It is commonly seen in pulp chamber rather than pulp canals.
- **Signs and symptoms**
 - No early clinical symptoms noticed in most of the cases.
 - The first evidence of the lesion is appearance of a pink-hued area on the crown of the tooth, which represents a hyperplastic and highly vascular pulp tissue filling the resorbed areas and is visible through the remaining overlying tooth substance. This appearance is known as *pink tooth of Mummery.*

Radiographic features

- The involved tooth exhibits a round or ovoid radiolucent area in the central portion of the tooth.
- Complete perforation of the tooth to the external surface is not a common finding, unless the condition is of such duration.

Histopathology

- The involved tooth shows a variable degree of resorption of the inner or pulpal surface of the dentine and proliferation of the pulp tissue filling the defect.
- Resorption is of irregular lacunar variety showing occasional osteoclasts or odontoclasts, hence the name *odontoclastoma.*
- The pulp tissue usually exhibits a chronic inflammatory reaction.
- As the resorptive process progresses, dentine may be completely resorbed in a narrow segment and sometimes, enamel is also resorbed, if the lesion is present in the coronal portion of the tooth.
- If the lesion is in the root of the tooth, perforation of both cementum and dentine may occur, which, if left untreated, may eventually result in complete separation of the apical portion from the remainder of the tooth.

Prognosis and predictive factors

- If perforation of the crown or root has not yet occurred, then root canal therapy can be carried out with a good prognosis.
- If perforation has already occurred, the tooth has to be extracted.
- In some cases, there may be spontaneous regression of the internal resorption occurred, with the lesion either remaining static or heals with actual repair by deposition of calcified tissue.

Hypercementosis

(Synonym: Cementum hyperplasia)
Hypercementosis is a non-neoplastic condition in which excessive cementum is deposited in continuation with the normal radicular cementum.

Aetiology

- The exact aetiology is unknown.
- The possible causes include:
 - Accelerated elongation of the tooth
 - Inflammation of tooth
 - Tooth repair
 - Osteitis deformans/Paget's disease of bone
- *Accelerated elongation of the tooth* owing to loss of an antagonist is accompanied by hyperplasia of the cementum, as a result to maintain the normal width of the periodontal ligament. It is more prominent at the apex of the root, although it usually involves the entire root, tapering off in thickness towards the cervical portion of the tooth.
- *Inflammation* at the apex of the tooth root occurs as a result of pulpal infection, sometimes stimulates excessive deposition of cementum. The deposition does not occur immediately next to the area of inflammation, since the cementoblasts and their direct precursors in this area have been degenerated as a result of inflammatory process. Instead, the cementum is laid down on the root surface at some distance above the apex, where it acts as a stimulus to cementoblasts.
- *Tooth repair* also causes deposition of cementum in a mild form, not to a remarkable amount. Occasionally, occlusal trauma results in mild root resorption. Such resorption and root fracture is repaired by the deposition of secondary cementum. Cemental tears or detachment of cementum strips from the root due to trauma are repaired by cementum

growing into and filling the defects, which eventually unite with the torn cementum.

- *Paget's disease of bone (osteitis deformans)* is a skeletal disease characterized by the generalized hypercementosis and apparent disappearance of the lamina dura of the teeth as well as by other features related to the bone itself.

Clinical features

- Single (localized form) or multiple teeth (generalized form) may be involved.
- Usually, thickness of cementum is increased in nonfunctioning teeth, which include embedded or impacted teeth.
- No significant clinical signs or symptoms will be present.
- No increase or decrease in tooth sensitivity.
- When the tooth with hypercementosis is extracted, the root appears larger in diameter than normal and its apex will be rounded.

Radiographic features

- Thickening of root cementum and apparent blunting of the roots are seen.
- The tooth root loses its typical sharpened and spiked or pointed apex.
- The diagnosis of hypercementosis is established by the shape or outline of the root rather than radiodensity.

Histopathology

- Excessive amount of secondary or cellular cementum is found deposited directly over the thin layer of primary acellular cementum.
- The area involved may be the entire root or only a portion, typically the apical region.
- The deposited secondary cementum has been termed as *osteocementum* because of its cellular nature and resembles to bone.
- This cementum is typically arranged in concentric layers around the root and frequently exhibits numerous deeply stained basophilic resting lines, which are parallel to the root surface.

Prognosis and predictive factors

- No treatment is required, since the condition is innocuous.
- Extraction of teeth is contraindicated, since the prognosis of such teeth is

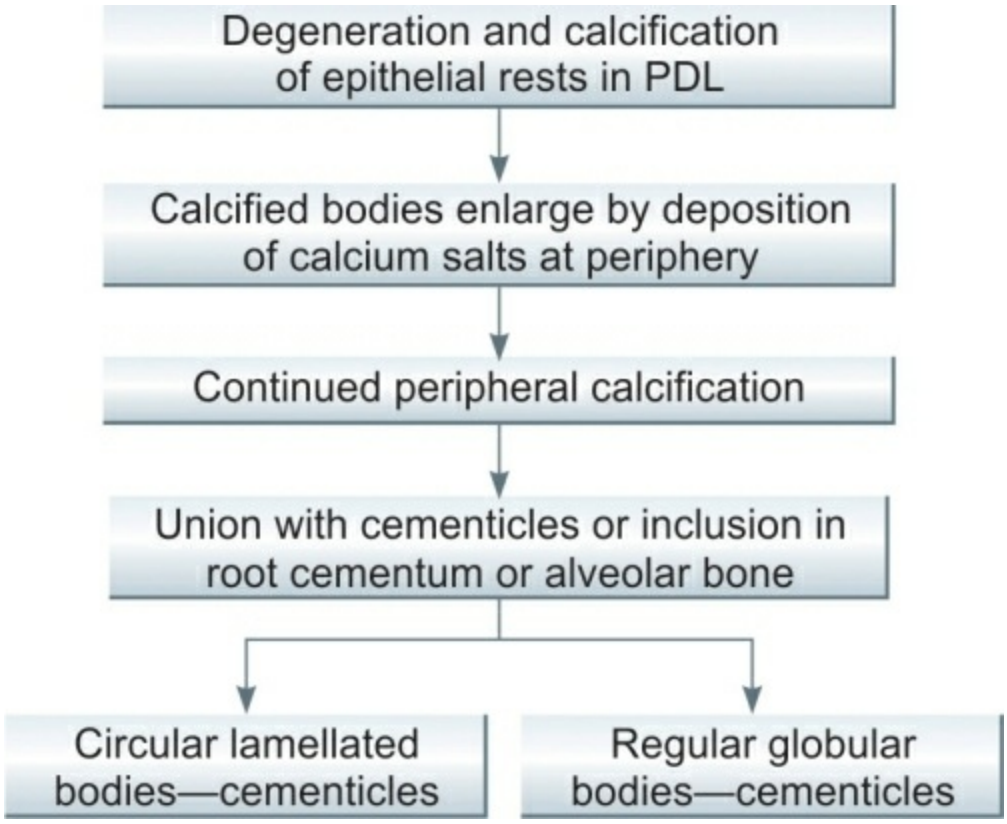
excellent in the absence of concomitant infection.
- Sometimes, hypercementosis causes obliteration of the periodontal ligament space causing ankylosis of tooth.

Cementicles

Cementicles are small foci of calcified tissue, which lie free in the periodontal ligament (PDL) of the lateral and apical root areas.

Pathogenesis

- The exact cause for cementicles formation is unknown.
- Cementicles may form in the ways as given in Flowchart 12.2.
- Cementicles may arise from focal calcification of connective tissue between Sharpey's bundles with no apparent central nidus. This calcification occurs as small round or ovoid globules of calcium salts.
- Cemental tear (small spicules of cementum torn from root surface) or fragments of bone detached from the alveolar plate may lie freely in the periodontal ligament, which may resemble cementicles, particularly after remodelling through resorption and subsequent repair.
- Cementicles may arise through calcification of thrombosed capillaries in the periodontal ligament.



FLOWCHART 12.2 Possible way of cementicles formation

Clinical features

Usually, cementicles are asymptomatic and are of no clinical significance.

Radiographic features

Even though cementicles are calcified materials, they may be too small to be seen in the intraoral radiograph, seldom being larger than 0.2–0.3 mm in diameter.

Histopathology

- These appear as dark basophilic structures, which may be circular laminated or amorphous globular bodies.
- These calcified bodies may lie free in the periodontal ligament or get attached to adjacent cementum (excementoses) or alveolar bone.
- Clusters of cementicles, which usually unite through interstitial deposition of bone or cementum at the root apex, are called *cementoma*.

Note: It is found that a variety of calcified bodies may occur in the periodontal ligament, not all of which have the morphological characteristics of cementum, but all are commonly known as *cementicles.*

Key points

- *Attrition* is defined as the physiologic wearing of tooth as a result of tooth-to-tooth contact as in mastication.
- *Abrasion* is the pathological wearing of tooth substance due to some abnormal mechanical process.
- *Erosion* is defined as irreversible loss of dental hard tissue by a chemical process that does not involve bacteria.
- *Abfraction* is the pathological loss of tooth structure from occlusal stress that creates repeated tooth flexure with failure of enamel and dentine at a location away from the point of loading.
- *Dental sclerosis* is a regressive alteration in tooth characterized by calcification of the dentinal tubules.
- *Pulp calcification* is a deposition of calcified mass(es) within the dental pulp for no apparent reasons.
- *Free pulp stones* may lie entirely within the pulp tissue and are not attached to dentinal walls.
- *Attached pulp stones* may be attached partial or completely to the dentinal walls.
- *Interstitial (embedded) pulp stones* are surrounded by reactionary or secondary dentine.
- *Hypercementosis*—possible causes include accelerated elongation of the tooth, inflammation of tooth, tooth repair and Paget's disease of bone.
- *Cementicles* are small foci of calcified tissue, which lie free in the periodontal ligament of the lateral and apical root areas.

Frequently asked questions

1. Attrition/abrasion/erosion/abfraction/tooth wasting diseases
2. Tertiary dentine
3. Pulp calcifications
4. Pulp stones
5. External resorption of teeth/internal resorption of teeth/pink tooth of mummery/odontoclastoma

6. Hypercementosis

CHAPTER 13

Healing of oral wounds

Healing is the body response to injury in an attempt to restore normal structure and function. The process of healing involves two distinct processes:

1. *Regeneration:* When healing takes place by proliferation of parenchymal cells and usually results in complete restoration of the original tissues.
2. *Repair:* When the healing takes place by proliferation of connective tissue elements resulting in fibrosis and scarring.

At times, both the processes take place simultaneously.

Regeneration of tissues

- In order to maintain proper structure of tissues, cells are under the constant regulatory control of their cell cycle. These include growth factors such as epidermal growth factor, fibroblast growth factor, platelet-derived growth factor, endothelial growth factor and transforming growth factor.
- Cell cycle is defined as the period between two successive cell divisions. It is divided into four unequal phases (Fig. 13.1):
 - *M (mitosis) phase:* Phase of mitosis.
 - *G1 (gap 1) phase:* The daughter cell enters G1 phase after mitosis.
 - *S (synthesis) phase:* During this phase, the synthesis of nuclear DNA takes place.
 - *G2 (gap 2) phase:* After completion of nuclear DNA duplication, the cell enters G2 phase.
 - *G0 (gap 0) phase:* This is the quiescent or resting phase of the cell after an M phase.
- Depending upon their capacity to divide, the cells of the body can be divided into three groups (Fig. 13.1):
 1. *Labile cells:* Labile cells continue to multiply throughout life under normal physiologic conditions and remain in the cell cycle always. These include surface epithelial cells of epidermis, alimentary tract, respiratory tract, urinary tract, vagina, cervix, uterine endometrium, haematopoietic cells of bone marrow and cells of lymph nodes and spleen. Labile cells are continuously dividing cells.

2. *Stable cells:* Stable cells decrease or lose their ability to proliferate after adolescence but retain the capacity to multiply in response to stimuli throughout adult life. These include parenchymal cells of organs like liver, pancreas, kidneys, adrenal and thyroid; and mesenchymal cells like smooth muscle cells, fibroblasts, vascular endothelium, bone and cartilage cells. Stable cells are in the resting phase (G0) but can be stimulated to enter the cell cycle.
3. *Permanent cells:* Permanent cells lose their ability to proliferate around the time of birth. These are neurons of nervous system, skeletal muscle and cardiac muscle cells. Permanent cells are nondividing cells which have left the cell cycle and die after injury.

- Regeneration of any type of parenchymal cells involves the following two processes:
 1. Proliferation of original cells from the margin of injury with migration to cover the gap.
 2. Proliferation of migrated cells with subsequent differentiation and maturation to reconstitute the original tissue.

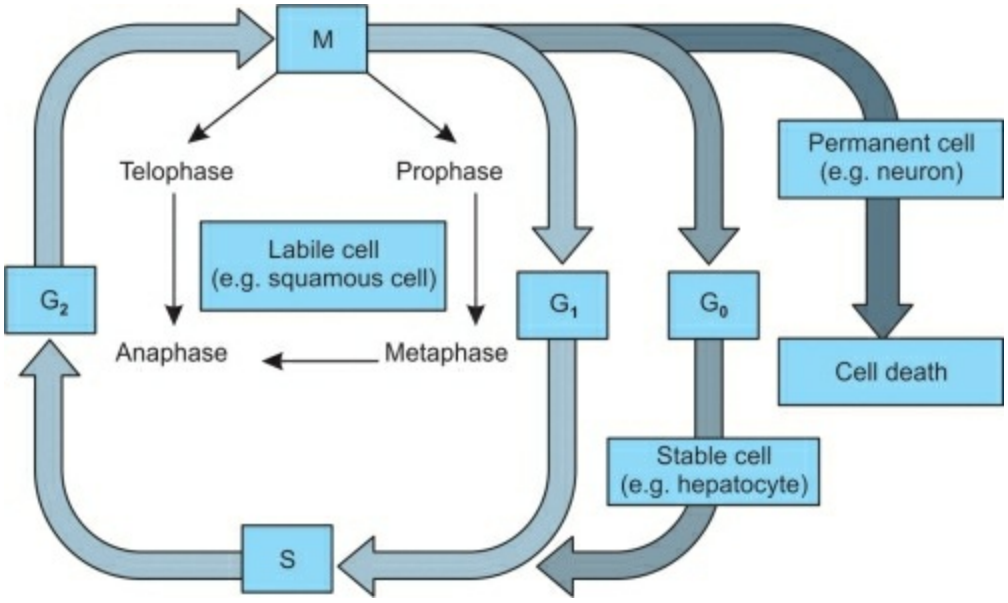


FIG. 13.1 Regeneration of tissues.

Repair of tissues

- Repair is the replacement of injured tissue by fibrous tissue. Two

processes are involved in repair:

1. Granulation tissue formation
2. Contraction of wounds

- Repair response takes place by participation of mesenchymal cells (consisting of connective tissue stem cells, fibrocytes and histiocytes), endothelial cells, macrophages, platelets and the parenchymal cells of the injured organ.

Granulation tissue formation

- The term *granulation tissue* derives its name from the slightly granular and pink appearance of the tissue. It corresponds to proliferation of new small blood vessels, which are slightly raised on the surface by thin covering of fibroblasts and young collagen.
- The following three phases are observed in the formation of granulation tissue:
 1. *Phase of inflammation:* Following trauma, blood clots at the site of injury. There is an acute inflammatory response with exudation of plasma cells, neutrophils and some monocytes within 24 hours.
 2. *Phase of clearance:* Combination of proteolytic enzymes liberated from neutrophils, autolytic enzymes from dead tissue cells, and phagocytic activity of macrophages clear off the necrotic tissue, debris and blood cells.
 3. *Phase of ingrowth of granulation tissue:* This phase consists of two main processes: (i) angiogenesis or neovascularization and (ii) fibrogenesis.
- *Angiogenesis (neovascularization):* Formation of new blood vessels at the site of injury takes place by proliferation of endothelial cells from the margins of severed blood vessels. Initially, the proliferated endothelial cells form solid buds but within a few hours develop a lumen and start carrying blood. The newly formed blood vessels are more leaky, accounting for the oedematous appearance of new granulation tissue. Soon, these blood vessels differentiate into muscular arterioles, thin-walled venules and true capillaries. The process of angiogenesis is stimulated with proteolytic destruction of basement membrane and takes place under the influence of the following factors:
 1. Angiogenesis takes place under the influence of vascular endothelial growth factor (VEGF) elaborated by mesenchymal cells but its receptors are present only in endothelial cells.

2. Platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), basic fibroblast growth factor (bFGF), other cytokines and surface integrins are the factors which are associated with cellular proliferation.

- *Fibrogenesis:* The newly formed blood vessels are present in an amorphous ground substance or matrix. The new fibroblasts originate from fibrocytes as well as by mitotic division of fibroblasts. Some of these fibroblasts have combination of morphologic and functional characteristics of smooth muscle cells (myofibroblasts). Collagen fibrils begin to appear by about sixth day of wound healing. As maturation proceeds, more and more of collagen is formed while the number of active fibroblasts and new blood vessels decreases. This results in the formation of scar known as *cicatrization*.

Contraction of wounds

The wound starts contracting after 2–3 days and the process is completed by the 14th day. During this period, the wound is reduced by approximately 80% of its original size. Contracted wound results in rapid healing since lesser surface area of the injured tissue has to be replaced.

Factors affecting the healing of oral wounds

The factors affecting the healing of oral wounds are as follows:

- **Severe trauma:** It interferes with rapid wound healing. Mild traumatic injury may favour the healing process.
- **Local temperature:** It influences the rate of healing, probably by its effect on local circulation and cell multiplication; thus in hyperthermia wound healing is accelerated, while in hypothermia wound healing is delayed.
- **Radiation:** The low doses of ionizing radiation stimulate healing, while large local doses of radiation or total body radiation tend to suppress healing. Exposure to ultraviolet radiation facilitates healing.
- **Circulatory factors:** Anaemia and dehydration have been reported to delay wound healing.
- **Nutritional factors:** Deficiency of protein and vitamins may affect healing of wound.
 - *Protein:* Protein deficiency causes delay in the appearance of new fibroblasts as well as decreased rate of fibroblasts multiplication in wounds.
 - *Vitamins*: Vitamin C or ascorbic acid acts through regulation of collagen

formation and formation of normal intercellular ground substance of the connective tissue. Vitamin A and D deficiencies also retard wound healing.

- **Age of the patient:** Wounds in younger people heal more rapidly than in elderly people. The exact cause is not known but probably it is related to general reduction in tissue metabolism, decreased circulatory efficiency and slowing of protein synthesis in elderly people.
- **Infection:** The wounds which are completely protected from bacterial infection heal considerably more slowly than wounds which are exposed to bacteria or other mild physical irritation. However, severe bacterial infection slows the healing of wounds.
- **Hormonal factors:** Adrenocorticotropic hormone (ACTH) and cortisone interfere with the healing process. In patients receiving ACTH or cortisone, the growth of granulation tissue is inhibited because of inhibition of new fibroblast proliferation, inhibition of new endothelial sprouts and reduction of the inflammatory reaction. Diabetes mellitus or insulin deficiency is one of the most widely recognized diseases characterized by delayed healing after surgical procedures including tooth extraction.
- **Miscellaneous factors:** These factors include:
 - Enzymes such as streptokinase, trypsin, alkaline phosphatase, coenzyme like adenosine-5-monophosphate
 - Growth-promoting factors, e.g. cartilage and mucopolysaccharides
 - Tissue extracts
 - Hydroxyproline
 - Hydrogen ion concentration
 - Electrolyte imbalance
 - Therapeutic agents, e.g. dilantin sodium, sulphonamides, antibiotics, anticancer drugs, immunosuppressive agents
 - Anticoagulants, e.g. heparin and dicoumarol
 - Sclerosing agents
 - Metals particularly trace elements, e.g. zinc, copper and deuterium oxide
 - Antigen–antibody reactions

Healing of oral soft tissue wounds (healing of biopsy wound)

Healing of oral wounds includes combination of both regeneration and repair. This can be accomplished in one of the following two ways:

1. Healing by first intention (primary union)
2. Healing by second intention (secondary union)

Healing by first intention (primary union)

- It includes healing of wounds, which have the following characteristics:
 - Clean and uninfected
 - Surgically incised
 - Without much loss of cells and tissue
 - Edges of wound are approximated by surgical sutures
- The sequence of events in primary union is described below:
 - **Initial haemorrhage:** Immediately after injury, the space between the approximated surfaces of incised wound is filled with blood which then clots and seals the wound against dehydration and infection.
 - **Acute inflammatory response:** This occurs within 24 hours after injury with appearance of polymorphs from the margins of incision. By third day, polymorphs are replaced by macrophages.
 - **Epithelial changes:** The basal cells of epidermis from both the cut margins start proliferating and migrating towards incisional space in the form of epithelial spurs. A well-approximated wound is covered by a layer of epithelium in 48 hours. The migrated epidermal cells separate the underlying viable dermis from the overlying necrotic material and clot. The basal cells from the margins continue to divide and form a multilayered new epidermis by fifth day, which is differentiated into superficial and deeper layers.
 - **Organization:** Fibroblasts and endothelial cells invade the wound area by third day. By fifth day, new collagen fibrils start forming which eventually coalesce into denser bundles and usually contract. In 4 weeks, small linear scar which may be depressed below the surface is seen.

Healing by second intention (secondary union)

- It includes healing of wounds, which have the following characteristics:
 - Open wound with a large tissue defect, at times infected.
 - Having extensive loss of cells and tissues.
 - The wound is not approximated by surgical suture but is left open.
- The basic events in secondary union are similar to primary union but differ in having a larger tissue defect which has to be bridged. Hence, healing takes place from the base upwards as well as from the margins

inwards. The healing by secondary intention is slow as compared to rapid healing of primary union.

- The sequence of events in secondary union is described below:
 - **Initial haemorrhage:** As a result of injury, the wound space is filled with blood and fibrin clot, which seals the wound against dehydration and infection.
 - **Inflammatory phase:** There is an initial acute inflammatory response followed by the appearance of macrophages.
 - **Epithelial changes:** As in primary healing, the epidermal cells from both the margins of the wound proliferate and migrate into the wound in the form of epithelial spurs till they meet in the middle and re-epithelialize the gap completely. However, the proliferating epithelial cells do not cover the surface fully until granulation tissue from base has started filling the wound space. In this way, pre-existing viable connective tissue is separated from necrotic material and clot on the surface forming *scab,* which is cast off. In time, the regenerated epidermis becomes stratified and keratinized.
 - **Granulation tissue:** The main bulk of secondary healing is by granulation tissue. It is formed by proliferation of fibroblasts and neovascularization from the adjoining viable elements. The newly formed granulation tissue is deep red, granular and very fragile. As the granulation tissue matures, it becomes white due to increase in collagen and decrease in vascularity.
 - **Wound contraction:** Contraction of wound is an important feature of secondary healing (but it is not seen in primary healing). Due to the action of myofibroblasts present in granulation tissue, the wound contracts to one-third to one-fourth of its original size. Wound contraction occurs at a time when active granulation tissue is being formed.
 - **Presence of infection:** Bacterial contamination of an open wound delays the process of healing due to release of bacterial toxins that provoke necrosis, suppuration and thrombosis. Surgical removal of dead and necrosed tissue *(debridement)* helps in preventing the bacterial infection of open wounds.

Complications of wound healing

- **Infection:** Wounds provide a port for entry of microorganisms. Infection of the wound delays the healing process. Usually, oral wounds heal

without any complications but systemic conditions such as diabetes mellitus, immunosuppressive state make the individual prone to infection.

- **Keloids and hypertrophic scars formation**
 - Keloids are overgrown scar tissues with no tendency for resolution. These occur in wounds, which heal without any complications. The common sites of occurrence include chest, back and shoulders.
 - Hypertrophic scars occur in wounds where healing is delayed. These are more cellular and vascular. The remodelling phase in these scars is prolonged. An imbalance between collagen production and degradation leads to excess of collagen in these scars. Clinically, these appear red, raised, itchy and tender. These become pale and flat as these mature. Spontaneous resolution may occur in course of time and this distinguishes them from keloids.

Note: Keloids and hypertrophic scars are not seen in the wounds of the oral cavity. In oral cavity, the wound remodelling rate is so high that even a normal scar is not seen usually.

- **Pigmentary changes:** These are common in healing of wounds on the skin and may appear as hypopigmented or hyperpigmented areas. Hypopigmented scars are not commonly seen in the oral cavity, whereas some lesions leave hyperpigmentation while healing (e.g. lichen planus, lichenoid reactions).
- **Cicatrization:** It refers to the late reduction in the size of the scar in contrast to immediate wound contraction. It is a complication seen in burns of the skin rather than in oral cavity.
- **Implantation cysts:** Epithelial cells may get entrapped in the wound and later may proliferate to form implantation cyst.
- **Healing after pulpal diseases:** Inflammation of pulp does not always result in pulpal necrosis. Healing of pulp depends on the degree of inflammation or infection, amount of pulp involved and the age of the patient. If the carious cavities are cleaned adequately and restored with suitable material, the abscess heals by reparative dentine formation and in few cases healing occurs by fibrosis.
- **Healing after periapical disease:** It may result in the formation of new

bone or fibrosis in the involved area. There will be a proliferation of fibroblasts and capillaries from the surrounding healthy connective tissue. Slowly the granulation tissue fills the entire defect. Osteoblasts appear in the deeper portions of granulation tissue and are gradually replaced by bone in the course of time.

Healing of extraction wounds

- Healing of extraction wound is very important for the dentist, since vast number of teeth is extracted because of pulp and periapical infection as well as periodontal disease.
- The healing of an extraction wound does not differ much from the healing of other wounds of the body except that it is modified by the peculiar anatomic situation, which exists after the removal of a tooth.

Immediate reaction following extraction

- After the removal of a tooth, the blood which fills the socket coagulates, red blood cells being entrapped in the fibrin meshwork and the ends of the blood vessels in the periodontal ligament become sealed off.
- The critical period is few hours after tooth extraction. If clot is dislodged, healing may be greatly delayed and may be extremely painful.
- Within the first 24–48 hours after extraction, a variety of phenomena occurs, which consist principally of alteration of vascular bed. There are vasodilatation, engorgement of blood vessels in remnants of periodontal ligament and mobilization of leukocytes to the immediate area around the clot.
- The surface of the blood clot will be covered by a thick layer of fibrin.
- The clot itself shows areas of contraction.

First week wound

- Within the first week after extraction, proliferation of fibroblasts from connective tissue cells in the remnants of the periodontal ligament is evident.
- These fibroblasts begin to grow into the clot around the periphery.
- This clot forms an actual scaffold upon which cells start to migrate.
- It is only a temporary structure and gradually gets replaced by granulation tissue.
- The epithelium at the periphery of the wound shows mild mitotic activity.

- The crest of the alveolar bone which forms the margin or neck of the socket exhibits the beginning of osteoclastic activity.
- Endothelial cell proliferation may be seen in the periodontal ligament area.
- During the period, blood clot begins to undergo organization by the ingrowth of fibroblasts and small capillaries from the residual periodontal ligament.

Second week wound

- During the second week after extraction of the tooth, the blood clot becomes organized by fibroblasts growing into the clot on the fibrinous meshwork.
- New delicate capillaries are penetrated to the centre of the clot.
- The remnants of the periodontal ligament gradually undergo degeneration.
- Sometimes, trabeculae of osteoid can be seen extending outward from the wall of the alveolus.
- Epithelial proliferation over the surface of the wound is extensive, although the wound is usually not completely covered, particularly in large posterior teeth.
- In smaller sockets, epithelialization may be completed.
- The margin of the alveolar socket exhibits prominent osteoclastic resorption.
- Fragments of necrotic bone, which may be fractured from the rim of the socket during extraction, are seen in the process of resorption of sequestration.

Third week wound

- As the healing process continues into third week, the original clot appears almost completely organized by maturing granulation tissue.
- Very young trabeculae of osteoid or uncalcified bone form around the entire periphery of the wound from the socket wall are seen.
- The early bone is formed by osteoblasts derived from pluripotential cells of the original periodontal ligament which assumes osteogenic function.
- The original cortical bone of the alveolar bone socket undergoes remodelling.
- The crest of the alveolar bone is rounded off by osteoclastic resorption.
- The surface of the wound may become completely epithelialized.

Fourth week wound

- During the fourth week after the extraction, the wound begins the final stage of healing.
- There is continued deposition and resorption of the bone filling the alveolar socket.
- Radiographic evidence of bone formation does not become prominent until the sixth or eight week after tooth extraction.
- The crest of the alveolar bone undergoes osteoclastic resorption during the healing process, so the crest of the healed socket is below that of the adjacent teeth.

Complications in healing of extraction wounds

Complications in healing of extraction wound include:
1. Dry socket
2. Fibrous healing of extraction wound

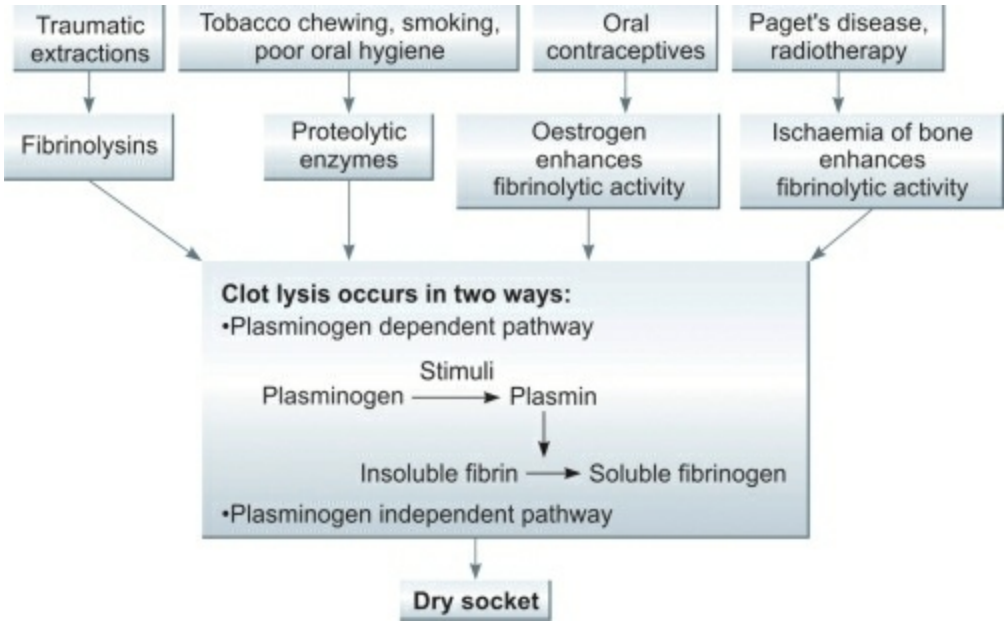
Dry socket

(Synonyms: Alveolitis sicca dolorosa; postoperative osteitis; alveolalgia; alveolar osteitis)

- It is the most common and painful complication in the healing of extraction wounds.
- It is a focal osteomyelitis in which the blood clot has disintegrated or been lost.

Pathogenesis

Flowchart 13.1 depicts the pathogenesis of dry socket complication in the healing of extraction wounds.



FLOWCHART 13.1 Pathogenesis of dry socket complication

Clinical features

- **Age.** Older age group.
- **Gender.** Female predilection.
- **Location.** Mandibular posterior region is commonly involved.
- **Signs and symptoms**
 - Foul smelling odour, severe throbbing pain and lymphadenopathy are commonly seen.
 - On occasion, the pain radiates from the socket to the ipsilateral ear, temporal region or eye.
 - Rarely trismus also may be noted.
 - Suppuration will not be evident.
 - The affected extraction site is filled initially with a dirty grey clot that is lost and leaves a bare bony socket (hence the name *dry socket*).
 - It usually starts by the second or third postoperative day and lasts for 7–10 days.
 - The diagnosis is confirmed by probing of the socket, which reveals exposed and extremely sensitive bone.

Prognosis and predictive factors

- All the sutures should be removed.
- The socket is irrigated with warm saline, followed by thorough clinical inspection of the socket for any unexpected pathosis.

- Curettage of the socket is not recommended because this typically increases the associated pain.
- Instruction for the patient to keep the socket clean via home irrigation with a chlorhexidine or saline solution is recommended.
- Use of an obtundent and antiseptic dressing such as iodoform gauze containing eugenol is controversial. Although the dressing may reduce the symptoms and help to keep out food debris, many believe the dressing acts as foreign material and delays healing of the extraction socket. If a dressing is used, then it should be changed every 24 hours for the first 3 days, then every 2–3 days until granulation tissue covers the exposed bone. The dressing should be discontinued as soon as the patient is free of pain.
- The antibiotics should not be used as topical applications, which may result in chronic foreign body reactions.
- Oral contraceptives, tobacco consumption, smoking and radiotherapy should be avoided few days before and after extraction.

Fibrous healing of extraction wound

- It is an uncommon complication, usually occurs following a difficult, complicated or surgical extraction of a tooth.
- The exact mechanism of formation is not known, but it occurs more frequently when the tooth extraction is accompanied by loss of both the lingual and labial or buccal cortical plates and periosteum.
- The lesion is usually asymptomatic.
- Radiographically, the lesion appears as a well-circumscribed radiolucent area in the site of a previous extraction wound.
- Histologically, the area of fibrous healing consists of dense bundles of collagen fibres with only occasional fibrocytes and few blood vessels. Little or no evidence of ossification is seen.

Healing of fracture

Healing of fracture

Fractures of the jaws are common injuries, and may range from minor alveolar process fracture to destructive injuries of the maxillofacial region.

Immediate effects of fracture

- When fracture of a bone occurs, the haversian vessels of the bone are torn at the fracture site.
- The resulting tissue damage evokes acute inflammation in the soft tissue adjacent to the fracture line, especially in the periosteal region, marrow spaces and the haversian canals.
- There is considerable extravasation of blood in this area and at the same time there is lack of local blood supply.
- The haversian canals of bone contain only a single vessel. When the flow of blood in this vessel is interrupted by tearing at the fracture site, the bone cells or osteocytes of the haversian system supplied by this vessel die. The dead bone extends away from the fracture area to the site of the anastomosing circulation.
- The blood clot formed first plays an important role in the healing of the fracture through the replacement by granulation tissue and its subsequent replacement by bone.

Callus formation

- *Callus* in Latin means *overgrowth of hard skin.*
- It unites the fractured ends of bone and it is composed of varying amount of fibrous tissue, cartilage and bone.
- The external callus consists of the new tissue which forms around the two fragments of bone on external surface.
- The internal callus is the new tissue arising from the marrow cavity.
- The periosteum is an important structure in callus formation and healing of the fracture.
- The cells immediately adjacent to the periosteum torn at the fracture line will usually die.
- Peripheral area of fracture line shows cellular activity within a few hours after the injury.
- The cells assume the features of osteoblasts and begin the formation of new bone at some distance from the fracture line within a few days after the fracture.
- The continued proliferation of osteogenic cells forms a collar of callus around or over the surface of the fracture.
- The new bone which begins to form in the external callus usually consists of irregular trabeculae often laid down at right angles to the surface of bone.
- Away from the fracture line, varying number of cells of the osteogenic

layer differentiates into chondroblasts rather than osteoblasts, which actually forms the cartilage. This cartilage fuses with the bone, although there is no sharp line of demarcation.

- As callus formation progresses, the cartilage cells begin to mature and the cartilage begins to calcify in a manner similar to normal endochondral bone formation. This calcification is prominently seen adjacent to the blood vessels. The calcified cartilage is gradually resorbed and replaced by bone.
- The new bone formed at the end of each fragment gradually unites and establishes continuity of the bone.

Remodelling of the callus

- The external and internal calluses, which unite the two fragments of bone, must be remodelled because there is always an abundance amount of new bone formed to strengthen the healing site.
- In addition, the new bone is frequently joined with fragments of the original dead bone.
- These fragments are slowly resorbed and replaced by a mature type of bone, which follows normal stress patterns.

Complications of fracture healing

- Delayed union
- Nonunion
- Fibrous union
- Lack of calcification

Replantation of tooth

Definition

- Replantation refers to the insertion of vital or nonvital tooth into the same alveolar socket from which it was removed or otherwise lost.
- This procedure is usually performed after traumatic injuries resulting in avulsion or other accidental loss of a tooth.
- Avulsion is severe form of tooth injury characterized by total displacement of tooth from the alveolar socket with damage to neurovascular bundles leading to loss of pulp vitality.
- A tooth can be replanted without root canal therapy, if root formation has

https://t.me/RoyalDentistryLibrary/

not been completed and the apex is open.
- In some cases, the pulp tissue will undergo necrosis within the short period.
- In other instances, there is apparent revascularization and reinnervation with establishment of vital pulp response.
- Preservation of the periodontal ligament is an important factor in successful retention of reimplanted teeth.
- The common finding is varying degree of resorption of cementum and dentine followed by subsequent replacement by bone resulting in ankylosis.
- When the tooth is avulsed, it is very important to reduce the extraoral time, in order to keep the periodontal cells viable for successful implantation.
- In such situations, a transport or storage medium is used to preserve the viability of periodontal ligament cells.
- Commonly used storage media are:
 - Milk
 - Saliva
 - Saline
 - Hanks balanced salt solution (HBSS)
 - Propolis
 - Viaspan
 - Coconut water (recently introduced storage media)

Healing after replantation of tooth

- After replantation, clot forms between the root surface and the ruptured periodontal ligament.
- Proliferation of fibroblasts and endothelial cells occurs in the periodontal ligament remnants on the alveolar bone side.
- The epithelium is reattached to the tooth at the end of the first week.
- Complete regeneration of the periodontal ligament takes place within 2–4 weeks.
- Superficial resorption of the root surface is repaired by new cementum deposition.
- Root resorption may or may not occur, it may begin within a matter of few weeks to months after replantation.
- If the process is extremely slow, then it takes place over a period of years.
- If the root resorption is rapid, then the tooth will be quickly exfoliated.

https://t.me/RoyalDentistryLibrary/

- Increased extraoral time or external damage to the periodontal ligament fibres results in ankylosis.
- Ankylosis as a result of fusion of alveolar bone and cementum of the tooth is seen.
- Progenitor cells with osteogenic potential from the adjacent bone marrow migrate to the root surface and lay down the bone in direct contact with the root creating ankylosis of tooth.

Transplantation of tooth

Definition

- Transplantation refers to the replacement of one damaged tooth by another tooth.
- The transplantation of teeth is mainly useful in replacement of teeth damaged beyond repair usually by dental caries.
- *Autotransplantation* means transplantation of the tooth in the same individual is more successful than allotransplants (transplantation from one person to another, of same species).
- Most common example of transplantation is replacement of mandibular first molar by a developing third molar.
- The criteria for a satisfactory transplantation are:
 - It should be capable of effective masticatory function.
 - It should maintain the physiological maxillary–mandibular and muscular relationship.
 - Aesthetically acceptable.
 - Stability.
 - Compatibility.
 - Normal colour and lustre of tooth should be usually maintained.
- Teeth with severe resorption of roots or extensive caries show poor prognosis.
- Homologous transplants of preserved frozen teeth have also been successfully carried out.
- It is recognized that replantation and transplantation of teeth are sufficiently established as procedures that can be utilized in the routine dental practice.

Key points

https://t.me/RoyalDentistryLibrary/

- *Healing* is the body response to injury in an attempt to restore normal structure and function.
- *Regeneration* when healing takes place by proliferation of parenchymal cells and usually results in complete restoration of the original tissues.
- *Repair* when the healing takes place by proliferation of connective tissue elements resulting in fibrosis and scarring.
- *Labile cells* continue to multiply throughout life under normal physiologic conditions and remain in the cell cycle always.
- *Stable cells* decrease or lose their ability to proliferate after adolescence but retain the capacity to multiply in response to stimuli throughout adult life.
- *Permanent cells* lose their ability to proliferate around the time of birth.
- *Healing by first intention (primary union):* Clean and uninfected wounds, surgically incised wounds, wound without much loss of cells and tissue and edges of wound are approximated by surgical sutures.
- *Healing by second intention (secondary union):* Open wound with a large tissue defect, at times infected, wounds having extensive loss of cells and tissues and edges of wound is not approximated by surgical suture but is left open.
- *Complications of wound healing:* Infection, keloid and hypertrophic scar formation, pigmentary changes, cicatrization, implantation cysts, healing after pulpal diseases and healing after periapical disease.
- *Dry socket* is a focal osteomyelitis in which the blood clot has disintegrated or been lost.
- *Replantation* refers to the insertion of vital or nonvital tooth into the same alveolar socket from which it was removed or otherwise lost.
- *Transplantation* refers to the replacement of one damaged tooth by another tooth.

Frequently asked questions

1. Discuss factors affecting the healing of oral wounds and add a note on healing of oral soft tissue wounds.
2. Healing of extraction wounds.
3. Dry socket.
4. Discuss the process and complications associated with healing of bone fracture.

https://t.me/RoyalDentistryLibrary/

https://t.me/RoyalDentistryLibrary/

CHAPTER 14

https://t.me/RoyalDentistryLibrary/

Metabolic disorders

Metabolism is defined as the sum total of tissue activity as considered in terms of physiochemical changes associated with and regulated by the availability, utilization and disposal of protein, fat, carbohydrate, vitamins, minerals, water and the influences which the endocrine exerts on these processes (Ducan, 1959).

Mineral metabolism

- Minerals are inorganic elements that are essential for life and provide both the structural and regulatory functions of the body.
- Although hormones are the primary regulators of metabolism, they are ineffective without minerals and vitamins.
- Calcium, phosphorus, magnesium, potassium, sodium, chlorine, iodine, copper, iron, zinc, manganese, cobalt, chromium, selenium and fluoride are the essential minerals for normal growth and development.
- *Macrominerals* or *principal elements* are nutritionally important minerals whose daily requirement is more than 100 mg. They include sodium, potassium, chloride, calcium, phosphorus, magnesium and sulphur.
- *Microminerals* or *trace elements* are those found in tissues in minute amounts but are found to be essential to life. Their requirement is less than 100 mg/day and they include chromium, copper, cobalt, iron, iodine, manganese, selenium, fluorine and zinc.

Calcium

- Calcium is the fifth most abundant element in the body.
- It forms hydroxyapatite crystals along with phosphorus, which forms the major structural support of the body (bones).
- The total amount of calcium present in our body is 100–170 g. 99% of calcium is found in the bones as carbonates or phosphates, while around 0.5% is present in soft tissue and 0.1% in extracellular fluid.
- The normal serum calcium level is 9–11 mg/dl.
- Three types of calcium are present in plasma, namely ionized calcium, protein-bound calcium and complexed calcium.
- Ionized calcium is a physiologically active form of calcium.

https://t.me/RoyalDentistryLibrary/

- The blood calcium level is largely controlled by the action of parathyroid glands.

Sources

Milk and milk products, green leafy vegetables, cabbage, beans, fruits, fish and egg yolk.

Daily requirements

- Daily dietary calcium intake:
 - 360 mg for newborn infants
 - 800 mg for children and adults
 - 1200 mg for pregnant or lactating and adolescent
- Calcium is taken in diet principally as calcium phosphate, carbonate and tartrate.

Absorption and excretion

- Citrates and lactose may lower the pH of the intestinal tract and aids in absorption of calcium.
- Oxalic acid interferes with calcium absorption by forming an insoluble calcium oxalate.
- Parathyroid hormone, vitamin D, thyroid, calcitonin and the steroid hormones have a direct effect on calcium metabolism.
- Calcium is excreted in both feces and urine. 80% of the total amount being excreted in the feces.

Functions

- Formation of bones and teeth
- Maintenance of skeletal structure
- Maintenance of tooth structure
- Normal membrane permeability
- Normal heart rhythm
- Neuromuscular excitability
- Coagulation of blood
- Muscle contraction
- Secondary or tertiary messenger

Deficiency

https://t.me/RoyalDentistryLibrary/

- The low concentration of calcium ions produces hyperirritability and tetany with characteristic carpopedal spasm, laryngospasm and convulsions.
- Hypocalcaemia is mainly due to hypoalbuminaemia followed by renal failure.
- High concentration of serum calcium level produces depressed nerve conductivity and muscle rigor.
- Hypercalcaemia is mainly due to primary hyperparathyroidism, malignancy and endocrine causes like acute adrenal insufficiency and renal failure.

Phosphorus

- Total body phosphorus content is approximately 500–800 g, of which 80–90% is in the skeletal system and 100 g is in the soft tissues.
- The major portions of phosphorus compounds are incorporated as phospholipids in cell membranes and nucleic acids.
- The normal inorganic phosphate level of blood ranges:
 - In adult: 2–4 mg/dl
 - In children: 3–5 mg/dl
- The blood phosphorus level is maintained by a balance of various factors such as parathyroid hormone, phosphate activity and vitamin D.

Sources

Milk, cereals, green leafy vegetables, meat and eggs.

Daily requirements

- In infants: 240 mg
- In adults: 800 mg
- In pregnancy and lactating women: Increase the daily dietary intake to 1200 mg

Absorption and excretion

- Absorption takes place in small intestine in the form of soluble inorganic phosphate.
- Excretion of phosphorus occurs primarily in urine.
- Phosphate uptake is sodium dependent, about 85% of filtered PO_4 is reabsorbed by the proximal tubules.

https://t.me/RoyalDentistryLibrary/

Functions

- Most of the body phosphorus is intimately associated with calcium in the metabolism of bones and teeth.
- Phosphates form an intermediate stage in the metabolism of fats and carbohydrates by phosphorylation.
- These are also utilized in the formation of phosphoproteins such as milk casein and in the formation of the nerve phosphatides and the nucleoproteins of cells.
- These provide energy-rich bonds in adenosine triphosphate compounds, which are important for muscle contraction.
- These form a part of coenzyme as pyridoxal phosphate used in decarboxylation and transamination of certain amino acids.

Deficiency

Deficiency is characterized by weakness, malaise, anorexia and bone pain.

Hypophosphatasia

- It is a hereditary disease transmitted as a recessive autosomal trait.
- There will be low level of serum alkaline phosphatase activity and elevated urinary excretion of phosphorylethanolamine, which results in defective bone matrix formation.
- **Clinical features**
 - *Symptoms:* Anorexia, irritability, persistent vomiting and mild pyrexia.
 - *Infantile form:* Severe hypocalcaemia, bone abnormalities and failure to thrive manifest the infantile form. Most of the cases are lethal.
 - *Juvenile form:* Hypophosphatasia of childhood is characterized by increased infection, growth retardation and rickets like deformities including deformed extremities, costochondral junction enlargement (rickety rosary) and pulmonary gastrointestinal and renal disorders.
 - *Adults form:* The adult form includes fracture with a prior history of rickets and osseous radiolucency.
 - *Skull:* Premature closure of skull sutures resulting in brachiocephalic appearance, increased intracranial pressure and gyral marking on internal surface of the skull.
- **Oral manifestations**
 - *Teeth*
 - Lack of cementum and periodontal attachment leads to poor support and premature loss of teeth.

https://t.me/RoyalDentistryLibrary/

- There is also delayed eruption of permanent teeth.
- Teeth may be hypoplastic.
- The pulp chamber and root canal are sometimes larger than normal.
- The roots either fail to develop fully or undergo early resorption of the apices.

- *Alveolar bone*: The alveolar bone fails to develop normally, which results in premature loss of primary teeth.

- **Radiographic features**
 - *Irregular ossification:* The metaphyses of long bones show spotty, streaky or irregular ossification.
 - *Skull:* Skull shows poor calcification.
 - *Beaten copper appearances:* Multiple radiolucent areas on skull called *gyral* or *convolutions* markings give *beaten copper appearance*, it results due to increased intracranial pressure.
 - *Lamina dura:* Thinning or loss of lamina dura and cortical bone is seen.
 - *Teeth:* Reduced enamel thickness, enlarged pulp chamber and root canal and presence of large pulp chamber as well as alveolar bone loss.

Magnesium

- Magnesium is the fourth most abundant and important cation in human body.
- It is extremely essential for life and is present as intracellular ion in all living cells and tissues.
- It is also necessary for the activity of certain enzymes such as phosphatase and carboxylase.
- The normal serum magnesium level is 1–3 mg/dl.

Sources

Cereals, nuts, beans, cabbage, cauliflower, meat, milk and fruits.

Daily requirements

- In infants: 50 mg
- In adults: 400 mg
- A daily increase of 150 mg is suggested during pregnancy and lactation.

Functions

- Magnesium is involved as a cofactor and as an activator of enzymatic

https://t.me/RoyalDentistryLibrary/

actions.
- It is essential for peptidases, ribonucleases, glycolytic enzymes and cocarboxylation reactions.
- It also exerts an effect on neuromuscular irritability.

Deficiency

- Magnesium deficiency is very rarely seen in humans.
- Its deficiency leads to disturbances in the neuromuscular and vascular system.
- It also affects teeth, liver and kidneys.
- The syndrome, human magnesium deficiency tetany, was first described by Valee et al in 1960.
- Clinically, patients show coma, severe neuromuscular hyperirritability, carpopedal spasm, athetoid movements and a positive Chvostek's sign.
- Hypermagnesium have been reported in uncontrolled diabetes mellitus, adrenocortical insufficiency, hypothyroidism, advanced renal failure and acute renal failure.

Pathological calcifications

- Pathological calcification implies the abnormal deposition of calcium salts along with iron, magnesium and other mineral salts.
- It is commonly classified as:
 - Dystrophic calcification
 - Metastatic calcification
 - Calcinosis

Dystrophic calcification

- In this type of calcification, the calcium salts are deposited in dead or degenerating tissues.
- The most common type of pathologic calcification found in wide variety of tissues.
- The most common sites include:
 - Areas of tuberculous necrosis
 - Blood vessels in arteriosclerosis
 - Scars
 - Fatty degeneration
 - Perineural connective tissue of the pulp

- There is no increase in the circulating serum calcium level in this type of calcification.
- Areas of dystrophic calcification may be found frequently in gingiva, tongue or cheeks.
- One of the most important common sites found is the pulps of the teeth.
- These are most commonly found in older individuals.
- These appear as fine fibrillar calcifications which may coalesce to form large masses of calcific material.
- Hill classified calcific degeneration of the pulp into two types:
 1. Nodular type: It is calcification of hyalinized connective tissue. It is usually perivascular or perineural and associated with increased fibrosis. It is most commonly found in the coronal portions of the pulp chamber.
 2. The second type of calcification is found in and around necrotic cells. It occurs in multicentric manner and is frequently found in the radicular portion of the pulp canal. It always shows a nidus in the centre.

Metastatic calcification

- In metastatic calcification, calcium salts are precipitated in previously undamaged tissues.
- This precipitation is due to an excess of blood calcium and occurs particularly in diseases such as hyperthyroidism, which depletes the bone calcium and causes a high level of blood calcium.
- It also occurs in hypervitaminosis D.
- The sites of occurrence are:
 - Kidneys
 - Gastric mucosa
 - Lungs
 - Tunica media of blood vessels

Calcinosis

- Calcinosis is the presence of calcification in or under the skin.
- There are two forms of calcinosis:
 1. *Calcinosis circumscripta:* Localized form
 2. *Calcinosis universalis:* Generalized form
- Calcinosis universalis is often associated with scleroderma and dermatomyositis.

Sodium

- In the human body, sodium is mainly associated with chloride as NaCl and $NaHCO_3$.
- The sodium ion content of normal 70 kg adult male ranges from 83 to 97 g.

Sources

Common salt, bread, whole grains, green leafy vegetables, nuts, eggs and milk.

Daily requirements

The minimal requirement of salt is about 0.5 g.

Absorption and excretion

- The kidney is the principal organ for the excretion of sodium.
- Sodium is also lost in profuse sweating.
- An inadequate intake or excessive loss of sodium stimulates the adrenal cortex to secrete aldosterone, a steroid hormone which acts directly on renal tubules to increase reabsorption and to conserve sodium.

Functions

- Maintenance of the acid–base balance as well as of osmotic pressure.
- Maintenance of proper intracellular sodium concentration, i.e. the sodium pump.
- It helps in maintaining the neuromuscular excitability, viscosity of blood and fluid balance.

Deficiency

- Sodium deficiency occurs in humans probably when diet contains very low sodium.
- It occurs in a severe or uncomplicated form, but it may be present as a sodium and chloride deficiency.
- When diets very low in salt are used for long period of time, it leads to:
 - Gradual weakness
 - Excessive fatigue
 - Lassitude
 - Apathy

- Anorexia
- Exhaustion
- Nausea
- Muscle cramps
- Peripheral vascular collapse

Potassium

- Potassium is the major intracellular cation commonly seen.
- It is widely distributed in:
 - Body fluid (blood and plasma)
 - Tissues—muscles, nerves as well as epithelial cells.
- The normal blood potassium level is about 4 mEq/l.

Sources

Banana, orange, pineapple, potato, beans, chicken, liver and tender coconut water.

Daily requirements

- Average requirement of potassium is 2–4 g daily.
- The requirement of potassium is greatest during the period of rapid growth of an individual.

Absorption and excretion

- Potassium is commonly absorbed in small intestine.
- About 90% of potassium is excreted in the urine.
- Potassium is also excreted in the gastrointestinal tract, saliva, bile, intestinal and gastric juices.

Functions

- The major functions of both potassium and sodium are carried out in coordination with each other.
- It influences the muscular activity, neuromuscular irritability and nerve conduction process.
- It is involved in the acid–base balance of body.
- It also has an important role in cardiac function.

Deficiency

- Deficiency of potassium may occur due to:
 - Gastrointestinal disorders
 - Malnutritional states
 - Administration of diuretics
 - Excessive cortisone or hydrocortisone dosage
 - Diabetic acidosis
- Death due to potassium deficiency occurs as a result of cardiac or respiratory failure
- Muscular irritability
- Muscular weakness
- Reduced or absent reflexes
- Mental confusion
- Paralysis
- Disturbances in conductivity and contractility of heart muscle

Hyperkalaemia

- It results from extensive tissue breakdown, adrenal insufficiency, advanced dehydration or administration of excessive amounts of potassium.
- Signs and symptoms include:
 - Mental confusion
 - Numbness
 - Tingling of the extremities
 - Pallor
 - Cold skin
 - Weakness
 - Disturbances in cardiac rhythm
 - Peripheral collapse

Trace elements

- Elements required in minute quantities to our body are usually considered as *trace elements.*
- Trace elements—iodine, copper, zinc, manganese, cobalt, chromium, selenium, fluoride, barium, strontium, silicon, vanadium, nickel and arsenic.
- *Bronze diabetes*: Iron overload can occur as a result of excessive iron absorption and is characterized by micronodular cirrhosis with marked brown pigmentation, diabetes mellitus and skin pigmentation.

- *Bantu siderosis*: It is a form of iron overload resulting from ingestion of home-made beer fermented in iron pots.

Disturbances in protein metabolism

- Proteins are complex biologic compounds of high molecular weight containing nitrogen, hydrogen, oxygen, carbon and small amounts of sulphur.

Protein requirements

- One gram of protein is required for each kilogram of body weight.
- Protein is required in increased quantity in the last half of pregnancy, lactation and in even greater amounts in infancy, childhood and adolescence.
- Protein and its constituent amino acids are of importance in the formation of hormones, enzymes, plasma proteins, antibodies and numerous other physiologically active substances.

Protein energy malnutrition (PEM)

It is a spectrum of diseases with kwashiorkor, whose essential feature is deficiency of protein to nutritional marasmus, which is due to severe and prolonged restriction of all food.

Amyloidosis

- An abnormal proteinaceous substance that is deposited between cells in tissues and organs of the body in a variety of clinical disorders is referred to as *amyloid.*
- By electron microscopy, X-ray crystallography and infrared spectroscopy, amyloid appears to be made up of non-branching fibrils with a characteristic β-pleated sheet configuration.

Forms of amyloid

- *Type A (secondary) amyloid* is a fibrillar protein of unknown origin that is seen in prolonged inflammatory disease, genetic diseases and syndromes such as familial Mediterranean fever.
- *Type B (primary) amyloid* is thought to be of immune origin because of its sequence homology with the NH_2 terminal end of immunoglobulin light

chain. Type B amyloid is most commonly seen in patients with multiple myeloma and macroglobulinaemia.

- *Type C amyloid* includes, amyloid of ageing, localized nonspecific amyloid and amyloid adjacent to APUD (amine precursor uptake and decarboxylase) tumours, i.e. pheochromocytoma.

Types

- *Primary amyloidosis:* There is no evidence of preceding or existing disease.
- *Secondary amyloidosis:* It is associated with various diseases.
- *Localized amyloidosis:* It is characterized by small localized deposits of amyloid in the skin, bladder and respiratory tract.
- *Familial amyloidosis:* It is a rare condition such as familial Mediterranean form or familial amyloidosis with polyneuropathy.
- *Hormone-related amyloid:* It is associated with tumours of endocrine cells, which secretes peptide hormones.

Causes

- Collagen diseases, e.g. rheumatoid arthritis
- Chronic infection, e.g. tuberculosis and osteomyelitis
- Regional enteritis
- Ulcerative colitis
- Malignant diseases like multiple myeloma, Hodgkin's disease and renal cell carcinoma

Clinical features

- The most commonly involved organs are kidneys, heart, gastrointestinal tract, liver and spleen.
- Amyloidosis is also seen in the respiratory tract, skin, eye, adrenals and nerves.
- Symptoms: Fatigue, weakness, ankle oedema, dyspnoea, paraesthesia, orthostatic hypotension and weight loss.
- Purpuric spots caused by haemorrhage result from amyloid deposits in the blood vessels.

Oral manifestations

- Fibrous glycoproteins are deposited in submucosa as well as in deeper muscular layers of tongue.

- Macroglossia: Amyloid deposition in tongue results in macroglossia. It is seen in both primary and secondary forms.
- There will be difficulty in chewing, swallowing or talking. The speech difficulties are due to paresis of the vocal cord resulting from deposit of amyloid in the upper third of larynx.
- Mobility of the tongue is reduced. Yellowish nodules are present along the lateral border of the tongue.
- Gingiva: It may be bluish, spongy and hypertrophied.

Histopathology

- Histopathologically, the deposition always begins between the cells and eventually surround and destroy the trapped native cells.
- It appears as a homogenous hyaline material and often perivascular in distribution.
- Under polarized light, the Congo-red-stained amyloid shows green birefringence. This reaction is shared by all forms of amyloid and is due to the crossed β-pleated configuration of amyloid fibrils.
- Amyloid A protein (AA) and amyloid light chain protein (AL) can be distinguished in histological sections as follows:
 - AA protein loses affinity for Congo-red after incubation of tissue sections with potassium permanganate; whereas AL proteins do not lose their affinity for Congo-red even after incubation with potassium permanganate.

Disturbances in carbohydrate metabolism

- Mucopolysaccharidoses (MPS) result from abnormal degradation of glycosaminoglycans such as dermatan sulphate, keratan sulphate, heparin sulphate and chondroitin sulphate resulting in organ accumulation and eventual dysfunction.
- Glycosaminoglycans or mucopolysaccharides are normally components of the cornea, cartilage, bone, connective tissue and the reticuloendothelial system.
- Deficiency of 10 catabolic enzymes of glycosaminoglycans or mucopolysaccharides gives rise to six distinct MPS (Table 14.1).
- In general, MPS are progressive disorders characterized by the involvement of multiple organs including the brain, liver, spleen, heart and blood vessels.

Table 14.1
Mucopolysaccharidoses

MPS	Disease	Enzyme deficient	Substance deficient	Clinical features
MPS I H	Hurler syndrome	α-L-iduronidase	Dermatan sulphate Heparan sulphate	Early clouding of cornea, grave manifestations, death usually before 10 years of age
MPS IS	Scheie syndrome	α-L-iduronidase	Dermatan sulphate Heparan sulphate	Stiff joints, cloudy cornea, aortic regurgitation, normal lifespan
MPS I H/S	Hurler–Scheie compound	α-L-iduronidase	Dermatan sulphate Heparan sulphate	Intermediate between MPS H and MPS S
MPS II A	Hunter syndrome, severe	Hunter corrective factor	Dermatan sulphate Heparan sulphate	No clouding of cornea, milder course than MPS H but death occurs usually before 15 years of age
MPS II B	Hunter syndrome, mild	Hunter corrective factor	Dermatan sulphate Heparan sulphate	Survival 30–50 years, fair intelligence
MPS III A	Sanfilippo syndrome A	Heparan sulphate sulphatase	Heparan sulphate	Mild somatic, severe central nervous system effects
MPS III B	Sanfilippo syndrome B	*N*-Acetyl-α-D-glucosaminidase	Heparan sulphate	Mild somatic, severe central nervous system effects
MPS IV	Morquio syndrome	Unknown	Keratin sulphate	Severe bone changes of distinctive type, cloudy cornea, aortic regurgitation
MPS V A	Maroteaux–Lamy syndrome, classic form	Maroteaux–Lamy corrective factor	Dermatan sulphate	Severe osseous and corneal change, normal intelligence
MPS V B	Maroteaux–Lamy syndrome, mild form	Maroteaux–Lamy corrective factor	Dermatan sulphate	Severe osseous and corneal change, normal intelligence
MPS VI	β-Glucuronidase deficiency	β-Glucuronidase	Dermatan sulphate	Hepatosplenomegaly, dysostosis, white cell inclusions, mental retardation

Hurler syndrome

(Synonyms: Mucopolysaccharidosis I; gargoylism)

- The excessive intracellular accumulation of both chondroitin sulphate B and heparan sulphate in many tissues and organs throughout the body including the liver, spleen, reticuloendothelial system, nervous system, cartilage, bone and heart.
- It is inherited as an autosomal recessive trait. A chromosomal abnormality occurs in chromosome arm 4p16.3.

Clinical features

- The disease usually becomes apparent within the first two years of life, progresses during early childhood and adolescence and terminates in

death usually before the puberty.

- The head appears large and the facial characteristics are quite typical consisting of prominent forehead, broad saddle nose, wide nostrils, hypertelorism, puffy eyelids, blushy eyebrows, thick lips, macroglossia and nasal congestion with noisy breathing.
- Progressive corneal clouding is a classical manifestation of the disease.
- Hepatosplenomegaly results in a protuberant abdomen.
- A short neck with spinal abnormalities is typical features, while flexion contracture results in the claw hands.

Oral manifestations

- Shortening and broadening of mandibles with prominent gonions
- Wide intergonial distance
- Localized areas of bone destruction in the jaws
- Hyperplastic dental follicles
- Gingival hyperplasia

Histological features

- Abnormal deposits are found in many sites with involved fibroblasts assuming the appearance of *clear cells* or *Gargoyle cells* or *Hurler cells.*
- The Hurler cells are relatively large with metachromatically staining cytoplasm which is either agranular of finely granular, often with crescent-shaped nuclei.
- Hurler cells are not identified with haematoxylin and eosin but they become evident with toluidine blue or with alcian blue or aldehyde fuchsin stains.
- In addition, *metachromatic granules* or *Reilly bodies* can be often demonstrated in the cytoplasm of circulating lymphocytes.

Disturbances in lipid metabolism

- Lipid metabolism is concerned with the assimilation, utilization, replacement and synthesis of the various fatty acids of the cells.
- All living cells contain fatty acids, largely in the form of esters with glycerol, cholesterol or other alcohols, or combined with phosphoric acids, nitrous bases or carbohydrates.

Classification of disorders

- *Nonlipid reticuloendotheliosis:* It is an inflammatory reticuloendothelioma condition with evidence suggesting that it may be reaction to some types of infection. There will be pathological accumulation in histiocytes and eosinophilic leukocytes. It includes:
 - Hand–Schuller–Christian diseases
 - Eosinophilic granuloma of bone (chronic localized histiocytosis X)
 - Letterer–Siwe diseases (acute disseminated histiocytosis X)
- *Lipid reticuloendotheliosis:* It is a disturbance in sphingomyelin and glucosyl ceramide metabolism:
 - Gaucher's disease
 - Niemann–Pick disease

Note

- Hand–Schuller–Christian disease: Both skeletal system and soft tissues are involved.
- Eosinophilic granuloma: Only bone is affected and soft tissues are rarely involved.
- Letterer–Siwe disease: It is an acute fulminating disease with involvement of both skeletal and extraskeletal tissues including the skin.

Hand–Schuller–Christian disease

(Synonym: Multiple focal eosinophilic granuloma)

It is characterized by skeletal and extraskeletal lesions and a chronic clinical course.

Clinical features

- **Age.** Usually before the age of 5 years and in young adults.
- **Gender.** Male predominance.
- **Location.** Skull, femur, ribs, vertebrae, pelvis, humerus and scapula.
- **Signs and symptoms**
 - Single or multiple areas of punched-out bone destruction in the skull is seen.
 - Unilateral or bilateral exophthalmos is present.
 - Diabetes insipidus with or without other manifestations of

dyspituitarism such as polyuria, dwarfism or infantilism is seen.
- Facial bone involvement frequently associated with soft tissue swelling and tenderness causes facial asymmetry.
- Otitis media is also common.
- Skin involvement exhibits papular or nodular lesions.

Oral manifestations

Sore mouth with or without ulcerative lesions, halitosis, gingivitis, severe bone loss, unpleasant taste, loose and sore teeth with precocious exfoliation of teeth and failure of healing of tooth sockets following extraction is seen.

Radiographic features

- The individual lesions particularly in the skull are usually sharply outlined, although the lesions in the jaws may be more diffuse.
- The lesions in the jaws are usually manifested as destruction of alveolar bone with tooth displacement.

Histopathology

It manifests in four stages during the progression of characteristic lesion:
1. A proliferative histiocytic phase with accumulation of collections of eosinophilic leukocytes scattered throughout the sheets of histiocytes.
2. A vascular granulomatous phase with persistence, if histiocytes and eosinophils, sometimes with aggregation of lipid laden (cholesterol) macrophages.
3. A diffuse xanthomatous phase with abundance of these foam cells.
4. A fibrous or healing phase.

Prognosis and predictive factors

- The prognosis is good.
- Approximately, half of the patients undergo spontaneous remission over a period of years.
- The most significant factors influencing the morbidity and mortality of the disease is the extent of the disease at the time of initial diagnosis and number of organ systems involved.

Eosinophilic granuloma

(Synonym: Unifocal eosinophilic granuloma)

It is primarily a histiocytic proliferation with an abundance of eosinophilic leukocytes but no intracellular lipid accumulation.

Clinical features

- **Age.** Older children and in young adults.
- **Gender.** Male predominance.
- **Location.** Skull, femur, ribs and humerus. Rarely develops from soft tissues of oral cavity.
- **Signs and symptoms**
 - Clinically, the lesion may present no physical signs or symptoms and may be found only upon an incidental roentgenographic examination of the bones of the head or other areas.
 - In some cases, localized swelling and tenderness may be present.
 - The lesions are destructive and well-demarcated, roughly round or oval in shape.
 - The area destroyed is replaced by a soft tissue depending upon the stage at which the lesion is examined.
 - The tissue of the early lesion is soft and brown in colour, since there is no necrosis. Later, the lesion becomes fibrous and greyish.

Radiographic features

- The lesions appear as irregular radiolucent areas usually involving superficial alveolar bone.
- The cortex is often destroyed and pathologic fractures may occur.

Histopathology

- The primary cell is the histiocytes, which grows in sheets or sheet-like collections.
- The histiocytes may coalesce and form multinucleated giant cells.
- The early lesions contain large number of focal collections of eosinophils.
- When the lesion matures, fibrosis occurs and eosinophils become less numerous and they may even disappear so that the lesion resembles Hand–Schuller–Christian disease.

Prognosis and predictive factors

- It is usually treated by surgical curettage and radiotherapy.
- Prognosis is good.

Letterer–Siwe disease

Letterer–Siwe disease is an acute, often fulminating histiocytic disorder which invariably occurs in infants, usually before the age of 3 years.

Clinical features

- The initial manifestation of this disease is often a skin rash involving the trunk, scalp and extremities.
- The rash may be erythematous, purpuric or ecchymotic, sometimes with ulcerations.
- Moreover, persistent low-grade spiking fever with malaise and irritability is seen.
- Splenomegaly, hepatomegaly and lymphadenopathy are early manifestations.
- Nodular or diffuse involvement of visceral organs, particularly the lungs and gastrointestinal tract.
- Diffuse involvement of the skeletal system also occurs.

Oral manifestations

- It consists of ulcerative lesions and gingival hyperplasia.
- Diffuse destruction of bone of the maxilla and mandible may occur, causing loosening and premature loss of teeth.

Histopathology

- Basically, histiocytic proliferation with or without eosinophils.
- These histiocytes do not contain significant amount of cholesterol so that foam cells are not the feature of disease.

Prognosis and predictive factors

- The prognosis of this disease is extremely poor.
- In most of the cases, the course of the disease is rapid and terminates fatally in a short period of time.

Gaucher's disease

- Gaucher's disease is a common lysosomal storage disease, characterized by the deposition of glucocerebroside in cells of the macrophage–monocyte system.

- Deficiency of specific lysosomal hydrolase and glucocerebrosidase, which cleave glucocerebroside to ceramide is held responsible for this disorder.

Clinical features

- **Age.** Adults and progress is slow.
- **Gender.** No sex predilection.
- **Signs and symptoms**
 - There will be enlargement of the lymph nodes, spleen and liver.
 - There may be bone pain due to changes in bone marrow.
 - There is often bleeding from the nose or gums. Teeth extraction from the affected area may result in bleeding complication.
 - CNS is commonly involved.
 - The skin is sometimes pigmented and the conjunctival fibrous tissue may be thickened and of brownish discolouration, a condition known as *pingueculae.*

Radiographic features

- Rarefaction: Bone changes occur due to destructive infiltration of the cerebrosidic reticulosis of the bone marrow. As a result of Gaucher's cells proliferation, the bone undergoes rarefaction.
- Porosity
 - There may be generalized porosity of the mandible and maxilla, with loss of trabecular structure.
 - Worm-eaten appearance: Pseudocystic radiolucent areas in the molars and premolars with worm-eaten appearances can be seen.

Histopathological features

- Examination of biopsy of spleen and liver shows typical Gaucher's cells, which are round pale cells, containing a small eccentric nucleus and wrinkled or crumpled silk cytoplasm.
- When the bone is involved, the bone marrow shows numerous large foamy, slightly granular cells with small round pyknotic nuclei—Gaucher's cells.

Prognosis and predictive factors

- The prognosis of malignant infantile form is very poor; the disease results in death usually within the first year of life.

- Administration of purified glucocerebrosidase results in a dramatic decrease in hepatic accumulations of glucocerebroside.

Niemann–Pick disease

(Synonym: Sphingomyelin lipidosis)

- It occurs due to lysosomal accumulation of sphingomyelin from inherited deficiency of sphingomyelinase.
- The mutant gene is localized to 18q11–12.
- Niemann–Pick disease can be classified as follows:
 - *Type A* is an acute infantile form.
 - *Type B* is a less common, chronic, non-neurological form.
 - *Type C* is a biochemically and genetically distinct form of a disease.
- Niemann–Pick disease type A is a severe infantile form with extensive neurologic involvement, marked visceral accumulation of sphingomyelin and progressive wasting resulting in early death within first 3 years of life.
- Niemann–Pick disease type B has a more variable course with the first symptom occurring in early childhood and many individuals survive till adulthood. In these patients, organomegaly is commonly seen but no nervous system involvement is noticed.
- Histologically, the affected cells become extremely enlarged secondary to the distention of lysosomes due to accumulation of sphingomyelin and cholesterol—*Niemann–Pick cells.* Niemann–Pick cells are foamy, lipid-laden cells distributed throughout the reticuloendothelial system. They are positive for cholesterol and alkaline phosphatase.
- Management: It is only symptomatic to control infection. Death occurs usually within 3 years of age. Enzyme replacement therapy and organ transplantation can also be done.

Disturbances in vitamin metabolism

- Vitamin is defined as an organic substance not made by the body, which is soluble in either fat or water and is needed only in minute quantities to act as a cofactor in a variety of metabolic reactions.
- Some of the vitamins occur in natural sources in a physiologically inactive form. These are called *provitamins.* These become active only after conversion within the animal.

Classification of vitamins

Vitamins are classified as follows:

- **Water-soluble vitamins**
 - Vitamin B complex
 - Vitamin B_1 (thiamine)
 - Vitamin B_2 (riboflavin)
 - Vitamin B_3 (niacin)
 - Vitamin B_5 (pantothenic acid)
 - Vitamin B_6 (pyridoxine)
 - Vitamin B_8 (biotin)
 - Vitamin B_9 (folic acid)
 - Vitamin B_{12} (cyanocobalamin)
 - Vitamin C (ascorbic acid)
 - Choline
 - Inositol
- **Fat-soluble vitamins**
 - Vitamin A
 - Vitamin D
 - Vitamin E
 - Vitamin K

Water-soluble vitamins

Water-soluble vitamins are essential coenzymes required in energy releasing mechanisms and in haemopoiesis. These act as coenzymes for metabolism of proteins, carbohydrates and fats.

B-complex vitamins

- Most of B-complex occurs in nature in the bound form within the cells of vegetables or animal tissues. The digestion for the liberation of vitamins and its absorption is a result of breakdown of cellular structures in the gut.
- Vitamin B-complex is not stored in appreciable amounts in the body tissues except vitamin B_{12}. Excretion of vitamins occurs in the kidney.

a. Thiamine (vitamin B_1)

- It is also known as *aneurin.*
- It was discovered by Eijkman in 1897.

- It is a colourless basic organic compound composed of a sulphated pyrimidine ring.

Sources

- Cereals: Wheat germ, wheat flour and rice bran.
- Pulses: Soybeans, split Bengal gram, lentil, moth, dry beans and split red gram.
- Vegetables: Lotus stems, capsicum and turnip greens.
- Nuts and oil seeds: Groundnuts, pistachio nuts and mustard seeds.
- Fruits: Apricots, pineapple and beat fruits.
- Meat: Whole meat, pork and liver sheep.
- Milk and milk products: Skimmed milk powder, cow's milk and khoa.

Daily requirements

- Men: 1.3 mg daily
- Women: 1.0 mg daily
- Children: 1.1 mg daily
- Pregnancy and lactation: 2 mg daily

Absorption and excretion

- It is readily absorbed from both small and large intestines.
- It is phosphorylated by the liver and kidneys.
- In tissues, it is found as thiamine pyrophosphate. Thiamine pyrophosphate is a coenzyme for decarboxylation of pyruvate to acetyl coenzyme A.
- Any excess supply of thiamine is excreted in the urine.

Functions

- Growth: It promotes growth, protects heart muscle and stimulates brain action.
- Nervous system: It plays an important role in the normal functioning of nervous system.
- Digestion: It aids in digestion especially that of carbohydrates.
- Diuretic: It is a mild diuretic and increases urine formation.
- GIT: It improves peristalsis and helps to prevent constipation.
- Blood cells: It maintains the normal blood count and improves circulation.
- Others: It also reduces fatigue, prevents premature ageing and senility by increasing mental alertness and promotes a healthy skin.

Deficiency.

Signs and symptoms

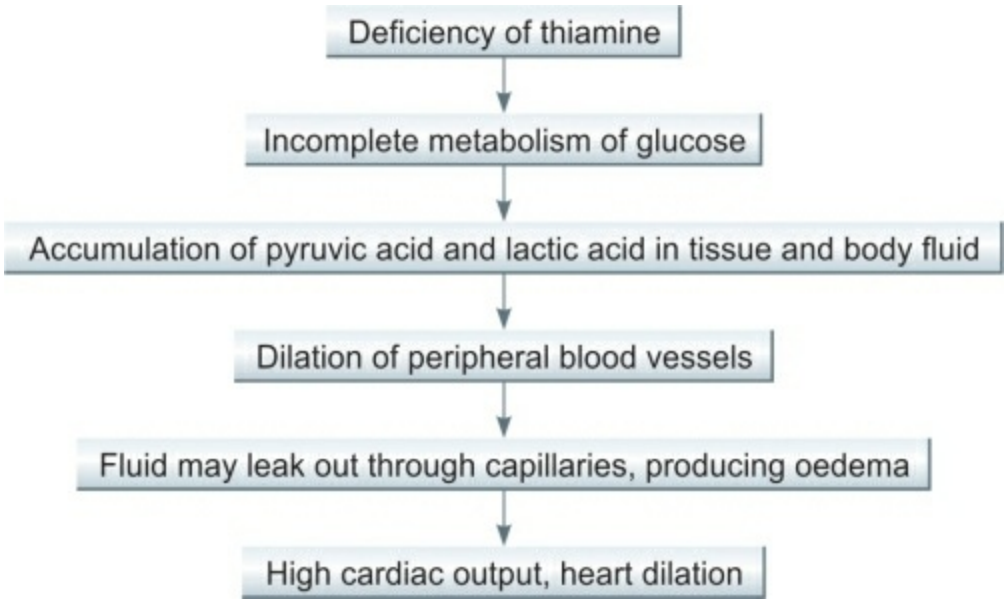
- Nervous disorders: Mental depression, nervous exhaustion and insomnia.
- Digestive symptoms: Loss of appetite, poor digestion, chronic constipation and loss of weight.
- Heart: Hypertrophy of the heart occurs due to accumulation of pyruvic acid and lactic acid.
- Beriberi: Prolonged deficiency of vitamin B_1 causes beriberi. There are two types of beriberi:
 1. Wet beriberi
 2. Dry beriberi
- Others:
 - Wernicke's encephalopathy
 - Korsakoff's psychosis

Beriberi

Wet beriberi

It is marked by cardiac dilation with four chamber enlargement, pallor and flabbiness of myocardium.

- **Aetiology**
 - Diet: It is caused due to polished rice diet.
 - Alcoholics: It is commonly seen in chronic alcoholics due to their poor nutrition in general and also because alcohol interferes with intestinal absorption of thiamine.
 - Others: It is often precipitated by infection, pregnancy and lactation.
- **Pathogenesis:** Pathogenesis of wet beriberi is depicted in Flowchart 14.1.
- **Clinical features**
 - Symptoms: Pain in legs after walking due to accumulation of lactic acid.
 - Cardiac signs: There is tachycardia and increased blood pressure, cardiomegaly, increased jugular venous pressure (JVP) and palpitations. There is also presence of sinus tachycardia and inverted T waves.
 - Skin: It is warm due to vasodilation.
 - Others: Oedema may develop rapidly to involve leg, face and trunk.



FLOWCHART 14.1 Pathogenesis of wet beriberi.

Dry beriberi

- **Clinical features**
 - It is a peripheral neuropathy.
 - In long-standing cases, there is degeneration and demyelination of both sensory and motor nerve fibres resulting in severe wasting of muscles.
 - Blood pyruvate levels will be normal.
 - Burning sensation of the oral mucosa and tongue is commonly seen.
- **Management**
 - Complete rest.
 - Thiamine 50 mg IM for 3 days, then 10 mg 3 times daily by oral route.
 - Infantile beriberi is treated via mother's milk. The mothers should receive 10,000 µg twice daily. In addition, infants should be given thiamine in doses of 10,000–20,000 µg IM once in a day for 3 days.

Wernicke's encephalopathy

- It is commonly seen in alcoholics with persistent vomiting.
- There is a classical triad of ocular abnormalities, ataxia and confusion.
- There are facial symmetrical areas of greyish discolouration.
- There is also bilateral symmetrical ophthalmoplegia and ataxia.
- Thiamine 50 mg by slow intravenous injection followed by 50 mg daily by oral route for 1 week is given.

Korsakoff's psychosis

- There is a predominant abnormality in mental function.
- There is profound impairment of memory recall and new learning ability.

b. Riboflavin (vitamin B_2)

- It is also called as the *beauty vitamin.*
- It is a yellowish green fluorescent compound soluble in water.
- The word *riboflavin* is derived from two sources, *ribose* refers to ribose sugar found in several vitamins and enzymes, and *flavin* means yellow.
- It is an essential component of coenzyme *flavin mononucleotide* and *flavin adenine dinucleotide,* involved mainly in a wide variety of oxidation-reduction reactions.

Sources

- Cereals: Wheat germ, rice bran, bajra and barley.
- Pulses and legumes: Soybeans, red gram, split green gram and peas.
- Vegetables: Lotus stems, turnip greens, spinach, cauliflower and brinjal.
- Nuts and oil seeds: Almonds, walnuts, chilgozas and mustard seeds.
- Fruits: Papayas, raisins, custard apples and jack fruits.
- Milk and milk products: Skimmed milk powder, cow's milk and whole milk powder.
- Animals: Liver of sheep, eggs, mutton and prawn.

Daily requirement

- Men: 1.5 mg daily
- Women: 1.2 mg daily
- Children: 1.3 mg daily
- Pregnancy and lactation: 2–2.3 mg daily

Absorption and excretion

- It is readily absorbed from the intestinal tract and is phosphorylated in the wall of the intestine.
- It is stored in the liver, kidneys and heart.
- Riboflavin is excreted primarily in the urine. Bile and sweat are the other minor routes of excretion.

Functions

- It is essential for growth and general health.
- Metabolism: It is involved in the metabolism of carbohydrates, fats and

proteins. It is essential for normal tissue maintenance.
- Nervous system: It helps for the functioning of nervous system.
- Digestion: It helps in digestion and prevents constipation.
- Eyes: It alleviates eye strain and is helpful in counteracting the tendency towards glaucoma.
- Others: It promotes a healthy skin, nails and hair, and strengthens the mucous lining of the mouth, lips and tongue.

Deficiency

Signs and symptoms

- It affects the nasolabial fold and ala of the nose which exhibits a scaly grey dermatitis and consists of enlarged follicles around the side of the nose which is plugged with dry sebaceous material.
- *Ocular changes:* It consists of corneal vasodilatation, photophobia and superficial and interstitial keratitis. There may be itching and burning of the eyes.
- *Skin and nails:* It may result in dull or oily skin, premature wrinkles on the face and split and brittle nails.
- *Others:* Malfunctioning of adrenal glands, anaemia, vaginal itching and cataract.

Oral manifestations

- *Tongue*
 - Glossitis begins with soreness of lip and lateral margins of the tongue.
 - Filiform papillae become atrophic while fungiform papillae remain normal or become engorged and mushroom-shaped giving the tongue a reddened coarse granular appearance.
 - In severe cases, the tongue becomes glazed and smooth due to complete atrophy of the papillae and exhibits magenta colour.
- *Lip*
 - Lips become red and shiny because of desquamation of epithelium.
 - Paleness of lips and cheilitis, which is seen as maceration and fissuring at the angle of the mouth.
 - As the disease progresses, angular cheilitis spread to the cheek, which may bleed easily and is painful if secondarily infected.

Management.

Riboflavin 25,000–50,000 μg is given daily in divided doses.

c. Niacin (vitamin B_3)

- It is also known as *nicotinic acid*.
- Niacin is required for the formation of coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which play an important role in redox reactions involving carbohydrate, protein and lipid metabolism.
- Deficiency of niacin leads to a disease called as *pellagra,* which means *rough skin*.

Sources

- Cereals: Rice bran, barley, wheat flour, jowar, wheat germ and finger mallet.
- Pulses and legumes: Peas, soybeans, red gram and split khesari.
- Vegetables: Turnip greens, beet green, carrot leaves and potatoes.
- Nuts and oilseeds: Groundnuts, sunflower, almonds and mustard seeds.
- Fruits: Apricots, passion fruit, custard apple and bael fruit.
- Animals: Liver of sheep, mutton, beef and prawns.
- Milk and milk products: Skimmed milk powder, cow's milk and whole milk powder.
- Tryptophan: Niacin can be endogenously prepared from tryptophan. 60 mg of tryptophan gives 1 mg of niacin.

Daily requirements

- Men: 17 mg daily
- Women: 13 mg daily
- Children: 15 mg daily
- Pregnancy and lactation: 12–15 mg daily

Absorption and excretion

- It is absorbed from both stomach and intestine, and stored in all tissues.
- It is excreted in the urine mostly as salts and to a smaller extent as free niacin.

Functions

- Nervous system: It is important for proper blood circulation and healthy functioning of the nervous system.
- Gastrointestinal tract: It is essential for the proper metabolism of proteins and carbohydrates.

- Blood vessels: It dilates the blood vessels and increases the flow of blood to the peripheral capillary system.
- Hormone: It is essential for the synthesis of sex hormone—oestrogen, progesterone and testosterone as well as cortisone, thyroxin and insulin.
- Others: It helps to maintain a normal healthy skin.

Deficiency.

Pellagra

- Causes:
 - Tryptophan deficiency.
 - Diet: Dietary deficiency of niacin. High dietary levels of amino acid leucine, antagonise the synthesis of NAD and NADP.
 - Miscellaneous: Chronic alcoholism, diarrhoea and carcinoid syndrome.
- Signs and symptoms
 - Prodromal symptoms: Loss of appetite, vague gastrointestinal disturbances and numbness or burning sensation in various locations will develop in 3 weeks.
 - It is called as disease of three D's:
 - **D**ermatitis
 - **D**iarrhoea
 - **D**ementia
 - Skin
 - *Erythematous rashes,* resembling severe sunburns, appear symmetrically on sunlight exposed parts of the body, especially on the neck.
 - In acute cases, skin lesions may produce vesiculation, cracking, exudation, crusting with ulceration and secondary infection.
 - In chronic cases, dermatitis occurs as roughening and thickening of skin with brownish pigmentation.
 - Alimentary tract
 - Anorexia, nausea, dysphagia and glossitis are seen.
 - Noninfective inflammation may extend through the gastrointestinal tract.
 - Diarrhoea is caused by atrophy of gastric epithelium followed by submucosal inflammation, which is then followed by ulceration.
 - Nervous system: Delirium is the most common mental disturbance in the acute form and dementia in chronic cases.
 - Others: Loss of appetite, irritability and burning sensation in different

areas of the body.

- Oral manifestations
 - Oral mucosa: Generalized fiery red and painful mucosa is seen.
 - Tongue
 - Desquamation of epithelium on dorsum of the tongue is commonly seen.
 - The filiform papillae are most sensitive and disappear first; the fungiform papillae may become enlarged.
 - Red, swollen and beefy tongue is seen.
 - In early stages, only the tip and margins of the tongue are swollen and red.
 - In advanced cases, the tongue losses all the papillae and the reddening become intense.
 - The mouth is sore and shows angular stomatitis and cheilitis.
 - Tenderness, pain and ulceration begin at the interdental papillae and spread rapidly.
 - Superimposed ANUG (acute necrotizing ulcerative gingivitis) or Vincent's infection involving the gingiva, tongue and mucosa is common.
- Management
 - Niacin 10 mg per day is advised.
 - Alcohol should be stopped.

d. Pantothenic acid (vitamin B_5)

- It was discovered by Roger Williams in 1933.
- It is a pale yellow oily liquid which can be crystallized readily with calcium and this is the form in which it is generally available in this form.

Sources

- Cereals: Oatmeal, toasted wheat germ, brown rice and wheat flour.
- Pulses and legumes: Soybean flour, split peas, lentil and black eye peas.
- Vegetables: Mushrooms, broccoli and cauliflower.
- Nuts and oil seed: Peanuts, sunflower seeds and cashew nuts.
- Meat: Calf liver.

Daily requirement

- Men: 10 mg
- Women: 10 mg

- Children: 5.5 mg

Absorption and excretion

- It is not destroyed in neutral solution.
- It is liable to destruction by food, processing techniques, caffeine, sulphur drugs, sleeping pills and alcohol.
- It is absorbed from the alimentary tract and excreted in urine and mother's milk.

Functions

- It is a part of enzyme system which plays a vital role in the metabolism of carbohydrates, fats and protein and in the synthesis of amino acids and fatty acids.
- It is also essential for the formation of porphyrins, the pigment portion of the haemoglobin molecule.
- It stimulates the adrenal glands and increases production of cortisone and other adrenal hormones.
- It is primarily used as an antistress factor and protects against most physical and mental stress.
- It increases vitality, ward off infections and fastens the recovery from ill health.
- It helps in maintaining the normal growth and development of the central nervous system.
- It prevents premature ageing and provides protection against any damage caused by excessive radiation.

Deficiency.

Signs and symptoms

- Muscle tissue: Chronic fatigue, muscle cramps, painful and burning feet and muscular weakness.
- Nervous system: Mental depression, irritability, dizziness and insomnia.
- Gastrointestinal: It may lead to gastric distress and constipation.
- Others: Increases tendency towards infection, greying and loss of hair, skin disorders, low blood sugar, low blood pressure and duodenal ulcer.

Management.

It is given in the dose of 1000 mg daily for 6 weeks.

e. Pyridoxine (vitamin B_6)

- It is an important coenzyme in the intermedullary metabolism of amino acids and complex glycolipids.
- It is a white crystalline substance, which is soluble in water and alcohol.

Sources

- Cereals: Wheat germ, brown rice, wheat flour and barley.
- Pulses and legumes: Soybeans, lentil and lima beans.
- Vegetables: Spinach, Brussels sprouts, potatoes and cauliflower.
- Nuts and oil seeds: Sunflower seeds, walnuts and chestnuts.
- Fruits: Bananas, avocados, prunes and raisins.

Daily requirements

- Adults: 2 mg
- Children: 1.7 mg
- Infants: 0.1–0.4 mg

Absorption and excretion

- It is absorbed mainly in the jejunum and ileum of the small intestine by passive diffusion.
- It is widely distributed in various tissues and excreted mainly from the kidney.
- Small quantities of vitamins are excreted in the feces and in sweat.

Deficiency.

Symptoms

- Nervous system: Peripheral neuropathy, mental retardation, irritability, mental confusion and nervousness.
- Blood: Anaemia, albuminuria and leukopaenia.
- Skin: Dermatitis and eczema.
- Others: Kidney stones, inflammation of the colon, damage to the pancreas, loss of muscular control, migraine headache and premature senility.

Oral manifestations

- Cheilosis: Cracking at the corner of the lip.
- Glossitis: Inflammation of the tongue.
- Others: Angular stomatitis, tooth decay and halitosis.

Management

10–50 mg daily in divided doses.

f. Biotin (vitamin B_8)

- It functions as a coenzyme for carbohydrate, fatty acid and amino acid metabolism.
- In the past, it was known as *vitamin H.*

Sources

- Cereals: Rice bran, rice polishing, rice germ, barley, oatmeal and brown rice.
- Pulses and legumes: Soybean flour, soybean, black-eyed peas and lentil.
- Vegetables: Mushrooms and cauliflower.
- Nuts: Walnuts, peanuts and almonds.
- Meat: Beef liver.

Daily requirements

- Adults: 100–200 μg
- Children: 50–200 μg

Functions

- Metabolism: It is involved in the metabolism of carbohydrates, proteins and fats.
- Hair: It is essential for the growth and health of the hair. It prevents premature greying of the hair as well as hair loss.
- Others: It helps to maintain the normal skin and nervous system. It controls proper distribution of colour pigments.

Deficiency.

Symptoms

- Skin: Scaly dermatitis, eczema, seborrhoea and prickling of the skin.
- Hair: It can cause alopecia and dandruff.
- Nervous system: Confusion and mental depression.
- Muscle: Muscular weakness, extreme fatigue and lassitude.
- Others: Anaemia, lack of appetite, hearing abnormalities and lung infections.
- Oral manifestations: Desquamation of the tongue.

Management

- 20 μg of biotin IM taken daily for 10 days can heal skin lesions.
- Oral biotin to be taken in amount of 400 μg daily for 8–12 weeks.

g. Folic acid (vitamin B_9)

- It is also known as *folacin* or *foliate*.
- It is a yellow crystalline substance sparingly soluble in water and acid solution.
- It undergoes rapid destruction when heated in neutral or alkaline substances.

Sources

- Cereals: Bajra, jowar, maize and wheat flour.
- Pulses and legumes: Cowpeas, whole Bengal gram, split Bengal gram, split green gram, split black gram and lentil.
- Vegetables: Spinach, cluster beans, ladies finger, curry leaves and French beans.
- Nuts and oil seeds: Gingelly seeds, groundnuts and coconuts.
- Meat and poultry: Eggs, liver of sheep and liver of goat.

Daily requirements

- Adults: 100 μg
- Children: 80 μg
- Pregnant women: 400 μg

Absorption and excretion

- It is absorbed along the entire length of intestine, although the jejunum of the small intestine is the primary site for its absorption.
- The major quantity of folic acid is stored in the liver.
- A small amount is excreted in the feces and urine but the additional amount is presumed to be metabolized and lost by desquamation of epithelial cells from the body surface.

Functions

- Red blood cells (RBCs): Folic acid in combination with vitamin B_{12} is essential for the formation, maturation and multiplication of RBCs.
- Nerve: It is necessary for the growth and division of all body cells, including nerve cells and for manufacturing a number of nerve

transmitters.
- Hair and skin: It is essential for the health of skin and hair, and helps to prevent premature greying of hair.
- Pregnancy: It is an important nutrient for the pregnant women and developing fetus. Folic acid also improves lactation.
- Others: It helps in building of antibodies which prevent and heal infection. It also produces nucleic acids, RNA and DNA.

Deficiency.

Causes

- Decreased intake: Inadequate diet, impaired absorption, malabsorption states and intrinsic intestinal diseases.
- Increased loss: Haemodialysis.
- Increased requirement: The body demands exceed the intake like in pregnancy, infancy, leukaemia, haemolytic anaemia.
- Others: Impaired utilization, diseases of the upper small bowel where folate is mainly absorbed and idiopathic.

Signs and symptoms

- Anaemia: Deficiency of folic acid causes anaemia, which often occurs in pregnant women and also in children.
- Skin: Loss of hair, greyish brown skin pigmentation can also occur.
- Reproductive disorders: Spontaneous abortions, difficulty during labour and high infant death can also occur. Loss of libido occurs in males.
- Nervous system: Dementia, mental depression and fatigue.

Oral manifestations

- Initially filiform papillae disappear and fungiform papillae remain prominent.
- In severe cases, fungiform papillae are lost and tongue becomes thick, smooth and fiery red.
- Severe ulcerative stomatitis may be seen.
- Swelling and redness of the lips and tongue are seen.

Management.

A daily dose of 5000–10000 μg of folic acid is sufficient and a maintenance dose of 5000 μg once in a week is given in cases of megaloblastic anaemia.

h. Cyanocobalamin (vitamin B_{12})

- Vitamin B_{12} is a complex organomatrix compound, also called *cobalamin*,

which is a cobalt containing porphyrin.
- It is freely soluble in water. It is resistant to boiling in neutral solution, but is liable to destruction in the presence of alkalis and acids.

Sources

- It is mostly found in the foods of 'animal origin'; therefore, vegetarians are advised to increase their intake of milk or take it in a tablet form as a supplement.
- Fish, meat and poultry: Sheep liver, goat liver, fresh shrimps, yolk eggs, goat meat, mutton, buffalo meat and whole eggs.
- Milk and milk products: Skimmed milk powder, buffalo milk, cow's milk and curd.

Daily requirements

- Adults: 1 μg
- Children: 0.2–1 μg

Absorption and excretion

- The sufficient quantity of gastric juice is essential for its absorption in the intestine.
- Calcium and protein-rich foods help in the absorption of this vitamin from the intestine.
- The large amount of this vitamin is stored in the liver.
- It is excreted in normal urine, stools and breast milk.

Functions

- RBCs: It is essential in the production and regeneration of RBCs.
- Nervous system: It improves concentration, memory and relieves irritability.
- Metabolism: It is necessary for the proper utilization of fats, carbohydrates and proteins. It is also used in the metabolism of folic acid.
- Others: It promotes growth and increases apatite in children.

Deficiency.

Causes

- Congenital deficiency without gastric atrophy is common.
- Systemic diseases: Diseases of terminal ileum, i.e. Crohn's disease.
- Defective absorption: Chronic atrophic gastritis with failure of intrinsic

factor production.

- Smoking: Smokers have lower levels of vitamin B_{12} and folic acid than non-smokers.
- Others: Inadequate diet and intrinsic factor deficiency.

Signs and symptoms

- Deficiency of vitamin B_{12} leads to megaloblastic anaemia or pernicious anaemia. However, pernicious anaemia is due to deficiency of intrinsic factor, which is essential for the absorption of vitamin B_{12} and hence deficiency of vitamin B_{12} also occurs.
- Generalized weakness, numbness and tingling sensation of the extremities are seen.
- Fatigue, headache, dizziness, nausea, vomiting, diarrhoea, loss of appetite, pallor and abdominal pain are seen.

Oral manifestations

- Painful tongue, glossitis and glossodynia are commonly seen.
- Tongue is inflamed and is beefy red in colour.
- Small shallow ulcers resembling aphthous ulcers on the tongue with atrophy of papillae and loss of normal muscle tone—Hunter's glossitis is seen.
- Fiery red appearance of tongue is seen due to inflammation and burning sensation.

Management

- Oral dose of 6–150 μg helps for the treatment of lack of concentration, fatigue depression, insomnia, anorexia, poor memory and loss of weight.
- Parenteral administration of 1000 μg of vitamin twice weekly helps in the treatment of anaemia.

2. Vitamin C

- It is also called as *ascorbic acid* or *antibiotic vitamin.*
- It is the most active reducing agent.
- It is a powerful antioxidant.

Sources

- Cereals, pulses and legumes: Red gram, peas, maize and Bengal gram.
- Vegetables: Parsley, drumstick leaves, turnip greens, cabbage, bitter gourd, radish leaves, carrot leaves, beet greens, cauliflower, cluster beans,

tomatoes, spinach and ladies finger.
- Nuts: Coconut and coconut milk.
- Fruits: Indian gooseberries, guavas, orange juice, limes, papayas strawberries, lemons, pineapples, custard apple, raspberry and mangoes.
- Fish and meat: Indian shark, Rohu fish, sheep liver and tengra fish.
- Milk and milk product: Khoa and skimmed milk power.

Daily requirements

- Adults: 40 mg
- Children: 40 mg
- Pregnant and lactating women: 80 mg

Absorption and excretion

- Absorption of ascorbic acid into the bloodstream takes place in the upper part of the small intestine.
- It is excreted by the kidney through the urine.

Functions

- Synthesis: It is important in the formation of collagen, chondroitin sulphate and neurotransmitter.
- Maintenance: It is useful for the maintenance of folate pool and mobility and phagocytic activity of neutrophils. It is also necessary for maintenance of bones and proper functioning of the adrenal and thyroid glands.
- Absorption: It enhances the absorption of iron in the body.
- Metabolism: Tryptophan, norepinephrine and tyrosine metabolism.
- Others: It promotes healing and protects against all forms of stress.

Deficiency.

Symptoms

- Mild deficiency—fatigue, anorexia, muscular pain and greater susceptibility to infection.
- Prolonged deficiency may cause scurvy.

Scurvy

- Prolonged deficiency of vitamin C may result in scurvy.
- It is characterized by:
 - Weakened blood vessels particularly microvessels having least muscular support.

- Defective synthesis of osteoid, which is derivative of collagen.
- Impaired wound healing.

- **Pathogenesis**
 - There is defective formation of collagen in connective tissue because of failure of hydroxylation of proline to hydroxyproline, which is a characteristic amino acid of collagen.
 - There will be increased permeability of capillary and anaemia due to erythropoiesis and defective collagen formation.
- **Clinical features**
 - Infantile scurvy: Lassitude, anorexia, painful limbs and enlargement of costochondral junction.
 - Folliculosis: Hair follicle rises above the skin and there are perifollicular haemorrhages, i.e. tiny points of bleeding occurring around the orifice of hair follicles with heaping of keratin-like material.
 - Haemorrhage
 - Haemorrhage may occur in the joint, into nerve sheath, under the nails or conjunctiva.
 - Petechial haemorrhage occurs in buttocks, abdomen, legs, arms, ankle and nailbeds.
 - Scorbutic child usually assumes a frog-like position and this may reflect as subperiosteal haemorrhage.
 - Epistaxis, anaemia and delayed wound healing.
 - Oedema of the limbs and face is a frequent finding in severe ascorbic acid deficiency.
- **Oral manifestations**
 - Interdental and marginal gingiva is bright red, swollen, smooth, shiny surface producing an appearance known as *scurvy bud.* In fully developed scurvy, the gingiva becomes boggy, ulcerated and bleeds easily.
 - Breath: Typical fetid breath of the patient with fusospirochetal stomatitis.
 - Severe cases: In severe cases, haemorrhage and swelling of periodontal ligament membrane occurs followed by loss of bone and exfoliation of teeth.
- **Histopathological features**
 - Osteoblasts fail to form osteoid.
 - Cartilage cells of epiphyseal plate continue to proliferate in normal fashion and salts are deposited in the matrix between the columns of

cartilage cells.
 - The wide zone of calcified but nonossified matrix called the *scorbutic lattice* develops in the metaphysis.
- **Management:** Vitamin C 250 mg three times daily can be given.

Fat-soluble vitamins

- These are soluble in fat.
- Bile salts are essential for their absorption.
- These are generally stored in the liver.
- These are not excreted in urine.

1. Vitamin A (retinol)

Carotene is a yellow pigment found in foods of both plant and animal origin. It is converted into vitamin A in the human body.

Sources

- Plant sources
 - Cereals and pulses: Red gram, soybeans, bajra and lentil.
 - Vegetables: Carrots, green leafy vegetables and spinach.
 - Fruits: Sweet potatoes, papayas, tomatoes, mangoes, persimmon and raspberries.
- Animal sources: Sheep liver, cow's milk, kidneys, fish liver oils.
- Fats and edible oils: Butter, hydrogenated oil and ghee.

Daily requirements

- Adults: 600 µg
- Pregnancy and lactation: 950 µg
- Children: 600 µg

Absorption and excretion

- Approximately 80% of vitamin A is absorbed in the human system.
- It is passed along with fat through the lymphatic system into the bloodstream.
- Absorption of vitamin A increases, if it is taken with fats.
- Absorption of this vitamin is poor in cases of diarrhoea, jaundice and abdominal disorders.
- Vitamin A, which is not absorbed, is excreted within 1 or 2 days in faeces.

Functions

- Epithelial tissue: Vitamin A helps in maintaining the integrity of epithelial tissue such as epithelial layer of skin, respiratory mucosa, oesophagus and gastrourinary tract.
- Structural integrity: It preserves the structural integrity and normal permeability of the cell membrane and membrane of intracellular organelles such as lysosomes and mitochondria.
- Bone and teeth: It accelerates the normal formation of bones and teeth.
- Vision: Vitamin A also has a specific role on the physiological mechanism of vision.
- Oxygenation: It also increases permeability of blood capillaries thereby contributing to better tissue oxygenation.
- Ageing and senility: It also prevents premature ageing and senility.
- Synthesis: It is required for the synthesis of glucocorticoids and cholesterol.

Deficiency. symptoms

- Effect on growth: Growth retardation and collagenous tissue formation is affected among young children.
- Effect on eyes: Night blindness, dry conjunctiva, Bitot's spot, corneal xerosis, corneal ulceration or keratomalacia can occur. Xerophthalmia due to decrease in lacrimal secretion is also seen.
- Keratinizing metaplasia: The epithelial cells fail to differentiate normally. The cells in the basal layer lose their specificity and tend to form a stratified squamous epithelium with keratin production. Keratinizing metaplasia of epithelial cells is usually evident in several organs such as bladder, vagina and skin and predisposes them to infection. Drying of skin and atrophy of sebaceous glands are commonly seen.
- Effect on reproductive organs: Degeneration of germinal epithelium causes sterility in males and cornification of vaginal epithelium in females.
- Effects on bone: Imbalance between osteoblasts (bone forming cells) and osteoclasts (bone resorbing cells) causing aberrations in the shape of the bone.
- Skin disorders: It may result in pimples, acne, boils and premature wrinkles.

Oral manifestations

- Teeth: Defective formation of enamel is commonly seen. Odontogenic

epithelium fails to undergo normal histodifferentiation and morphodifferentiation, which results in increased rate of cell proliferation. Therefore, epithelial invasion of pulpal tissue is characteristic feature of vitamin A deficiency.

- Hypoplasia of teeth: The enamel forming cells are usually affected by vitamin A deficiency, which results in the formation of poorly calcified enamel matrix.
- Dentine: Lack of normal tubular arrangement and vascular and cellular inclusions in dentine is seen.
- Eruption: Delayed or cessation of eruption is seen in prolonged deficiency.
- Gingiva: In prolonged deficiency, gingival epithelium becomes hyperplastic and hyperkeratinization.
- Salivary gland: Major and minor salivary glands undergo typical keratinizing metaplasia.

Management: Depending upon deficiency symptoms, vitamin A is given in the dose of 7500–15,000 μg per day for 1 month.

2. Vitamin D

- It is also called as *the sunshine vitamin.*
- Vitamin D (1,25-dihydroxycholecalciferol) is one of the compound that are grouped together as the hydroxylated cholecalciferol.
- If vitamin D deficiency occurs in children and infants, it is called as *rickets*, and if it occurs in adults, it is called as *osteomalacia*.

Forms

- D_3: It is present in fish liver oils and animal fats, and is called *cholecalciferol*.
- D_2: It is obtained artificially by irradiation of ergosterol, and is called *ergocalciferol*.

Sources

- Fish and poultry: Cod liver oil, shark liver oil and eggs.
- Fate and edible oils: Ghee and butter.
- Sunlight: It is the most important source of the vitamin D.

Daily requirements

- Infants and children: 0.01 mg

- Adults: 0.01 mg
- Pregnancy and lactating women: 0.01 mg

Absorption and excretion

- Bile and fat are essential for the absorption of vitamin D.
- The vitamin is absorbed from the jejunum of the small intestine and is transported in the lymph as chylomicrons to the bloodstream.
- Excretion of vitamin D and its metabolites occurs primarily through the feces.

Functions

- Maintenance: Vitamin D helps in the maintenance of normal plasma levels of calcium and phosphorus.
- Teeth and bone: It plays an important role in the proper formation of teeth and bones.
- Thyroid gland: Vitamin D is necessary for the healthy functioning of parathyroid gland, which regulates the calcium levels in the blood.

Deficiency (table 14.2).

Rickets: The word *rickets* refers to any disorder occurring due to deficiency of vitamin D–calcium–phosphorus axis, which results in hypomineralized bone matrix, i.e. failure of endochondral calcification.

- **Clinical features**
 - Age: It occurs in infants and children. In the first 6 months of life, tetany and convulsions are common manifestations due to hypocalcaemia.
 - Craniotabes: Formation of indentations due to placement of fingers on localized thin areas on skull is known as *craniotabes*.
 - Extremities: Patients have a short stature and deformed extremities. Children with rickets show bowing of legs.
 - Head: Frontal bossing and brachycephalic appearance are seen.
 - Rickety rosary: It is a deformation of chest results from overgrowth of cartilage or osteoid tissue at the costochondral junction.
 - Pigeon breast: The weakened metaphyseal areas of the ribs are pulled by the respiratory muscles and thus bend inwards creating anterior protrusion of the sternum resulting in a pigeon breast deformity.
 - Harrison grooves: The inward pull at the margins of diaphragm creates Harrison's grooves—girdling the thoracic cavity at the lower margin of

the rib cage.
 - Lumbar lordosis: When an ambulatory child develops rickets, deformities are likely to affect the spine, pelvis and long bones causing *lumbar lordosis.*
- **Oral manifestations**
 - Teeth: Developmental abnormalities of dentine and enamel, delayed eruption and malalignment of teeth are seen.
 - Enamel: Enamel may be hypoplastic, mottled, yellow grey in colour.
 - Pulp: Large pulp chamber, high pulp horns and delayed closure of root apices are seen.
 - Malocclusion: The osteoid of alveolar bone (formed during remodelling) is so soft that the teeth are displaced, and it causes malocclusion.
- **Radiographic features**
 - Long bones
 - The earliest and prominent manifestation is widening of epiphysis of the long bones.
 - Bowing is a characteristic deformity seen in the weight-bearing areas and fine trabeculae are reduced in number.
 - Green stick fractures will be noted in many cases.
 - Jaw bones
 - Thinning of cortical structures of jaw such as inferior mandibular canal, lamina dura and follicular walls of developing teeth has been noted.
 - Trabeculae of jaws are thin and sparse.
 - In severe cases, diffused radiolucency is seen in the jaws.
 - Teeth
 - If the disease occurs before 3 years of age, enamel hypoplasia is fairly common.
 - The pulp cavities of deciduous teeth are grossly enlarged.
 - The dentine is reduced to a thin margin separating the pulp cavity from enamel and cementum.

Table 14.2

Causes and mechanisms of vitamin D deficiency

Predisposing factors	Mechanisms
Dietary lack of meat and dairy product	Low levels of vitamin D in the diet
Lack of adequate exposure to ultraviolet light	Failure of vitamin D precursor synthesis in the skin
Gastric intestinal disease or chronic liver disease	Malabsorption of vitamin D and calcium
Aluminium toxicity and biphosphonates	Direct inhibition of bone mineralization
Administration of anticonvulsant drug like phenobarbitone	These drugs enhance liver enzyme activity which results in increased breakdown of vitamin D to biological inert product
Chronic renal failure	Reduced conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$
Hypophosphataemia rickets (X-linked dominant)	Inherited defect in renal tubular phosphate reabsorption leading to hypophosphataemia
Hypophosphatasia (autosomal recessive)	Defect mutation in bone alkaline phosphatase which causes inhibition of bone mineralization at the calcification front

Osteomalacia

- It is also known as *adult rickets.*
- Only flat bones and diaphyses of long bones are affected.
- It is most commonly seen in postmenopausal females with a history of low dietary calcium intake and little exposure to UV light.
- **Clinical features**
 - Age: 40–60 years.
 - Sex: Females are commonly affected.
 - Bone: Remodelling of bone causes softening and distortion of the skeleton due to calcium deficiency.
 - Symptoms: The majority of patients have bone pain and muscle weakness of varying severity.
 - Others: There is increased tendency towards fracture, peculiar waddling or penguin gait, tetany and greenstick bone fractures.
- **Oral manifestations:** There is incidence of severe periodontitis in some cases of osteomalacia.
- **Radiographic features**
 - Pseudofracture: Usually, a poorly calcified ribbon-like zone extending into bone at approximately right angles to the periosteal margin is seen. It may be partial or complete fracture without displacement in which callus has been formed but there is no calcium available to be deposited, thus healing process is not complete and fracture remains apparent radiographically. It is also called as *Looser's zone.*

- Jaws: Pseudofracture of the jaws near the angle has also been noted.
- Bone: Bony trabeculae may be sparse and unusually coarse in intraoral periapical radiograph.
- Lamina dura: The lamina dura may be thin or absent in long-standing and severe cases of osteomalacia.

- **Management of rickets and osteomalacia**
 - Dietary enrichment of vitamin D in the form of milk.
 - If tetany is present, daily dose of 1000–2000 IU of calcium gluconate is given in combination with 500–1000 mg of calcium.
 - Curative treatment includes 2000–4000 IU of calcium daily for 6–12 weeks followed by a daily maintenance dose of 2000–4000 IU for a prolonged period.
 - Patients with osteomalacia due to intestinal malabsorption require a larger dose of vitamin D and calcium, i.e. 40,000–100,000 IU of vitamin D and 15–20 g of calcium lactate per day.

3. Vitamin E (tocopherol)

- It is also called as *anti-ageing factor*.
- The word *tocopherol* is derived from the word *tocos* meaning *child birth* and *pheros* meaning *to bear*.
- It is yellow, oily liquid freely soluble in fat solvents.
- It is not destroyed by heat even at room temperature or above 100°C. It is destroyed by UV light.

Sources

- Vegetable oils: The richest sources of vitamin E are crude vegetable oils, especially wheat germ, sunflower seeds and soybean oil.
- Cereals: Raw sprouted seeds and grains, especially whole wheat are moderate sources.
- Animals: Meats and eggs are minor sources of vitamin E.

Daily requirements

- Men: 8–10 mg
- Women: 5–8 mg
- Children: 8.3 mg

Absorption and excretion

- Vitamin E in the diet is absorbed from the gastrointestinal tract by a

mechanism similar to that of other fat-soluble vitamins.

- It enters the bloodstream via the lymphatic system.
- About one-third of the vitamin is excreted in the bile and the remaining is excreted in the urine.

Functions

- Reproductive function: Vitamin E protects reproductive system and prevents sterility. All the three layers of embryo—ectoderm, mesoderm and endoderm, are preserved by vitamin E.
- Blood flow and clotting mechanism: Vitamin E dilates the capillaries and enables free blood flow through them. It also dissolves the blood clot and prevents clot formation.
- Electron transport system: It functions as a cofactor in the electron transport system.
- Healing: It prevents the formation of scar tissue and in some instances it clears formed scar tissue also.

Deficiency. symptoms

- Reproductive: Abortion of fetus in females and atrophy of spermatogenic structures in males leading to permanent sterility.
- Muscles: It causes degenerative changes in muscles.
- Heart: Vitamin E deficiency causes necrosis and fibrosis of heart muscles.
- Blood capillaries: Deficiency may lead to degenerative changes in the blood capillaries which in turn lead to heart and lung diseases, pulmonary embolism and brain stroke.

Oral manifestations: Loss of pigmentation and enamel hypoplasia are seen.

Management: Vitamin E is given in the dose of 100–400 mg daily.

4. Vitamin K (phylloquinone)

- It is essential for the production of prothrombin and other factors, which are involved in the blood clotting mechanism, hence it is known as *anti-haemorrhagic vitamin.*
- It is not easily destroyed by light, heat or exposure to air. It is destroyed by strong acids, alkalis and oxidizing agents.

Sources.

Vegetables: Kale, turnip greens, spinach, broccoli, cabbage, lettuce, asparagus

and pepper.

Requirements

- *Adults:* 70–140 μg
- *Children:* 35–75 μg

Functions

- Synthesis: It is essential for the hepatic synthesis of coagulation factors II, V, VII, IX and X.
- Clotting: It prevents haemorrhage by clot formation through production of prothrombin.
- Oxidative phosphorylation: It acts as a cofactor in oxidative phosphorylation associated with lipid.

Deficiency. signs and symptoms

- Prolongation of clotting time and a tendency to bleed profusely are seen.
- Frequent nasal bleeding will be present.

Oral manifestations: Gingival bleeding is commonly seen.

Management: Vitamin K is given in the dose of 10–20 mg daily.

Diseases of pituitary gland

Hyperpituitarism

It results from hyperfunction of anterior lobe of pituitary gland, most significantly with increased production of growth hormone (GH). GH acts directly on some tissues but most of its biological effects are accounted by stimulation of secretion of insulin-like growth factor I (IGF-I).

Types

- *Gigantism:* It occurs due to increased production of GH before the closure of epiphysis of the long bones.
- *Acromegaly:* It occurs due to increased production of GH after the closure of epiphysis of the long bones.

Clinical features

Gigantism

- Generalized enlargement of the soft tissue and bones is commonly seen.
- It may show genital underdevelopment and excessive perspiration and patient may complain of headache, lassitude, fatigue, muscle and joint pain and hot flashes.
- Calvarium will be increased in size.
- Pituitary tumours may also induce deficiency of other pituitary hormones causing signs of hypogonadism including decreased libido and menstrual problems in women.

Acromegaly

- It is more common in males and occurs frequently in the third decade.
- Bone overgrowth and thickening of the soft tissue cause a characteristic coarsening of facial features.
- Hand and feet become large, with clubbing of the toes and fingers due to enlargement of the tufts of the terminal phalanges.
- Temporal headache, photophobia and reduction in vision are commonly seen.

Oral manifestations

- Teeth

- Macrodontia is commonly seen.
- The teeth become spaced because of enlargement of the tongue and disproportionate enlargement of the two jaws.

- Jaw bone
 - Mandibular condylar growth is very prominent.
 - Mandibular prognathism—pronounced class III malocclusion.
 - The palatal vault is usually flattened and the tongue increases in size and may cause crenation on its lateral border.
 - Lips become thick and Negroid.

Radiographic features

- Skull
 - Enlargement of sella turcica, enlargement of paranasal sinus and excessive pneumatization of temporal bone are seen.
 - Enlargement and distortion of the pituitary fossa is also seen.
 - Air sinuses are prominent in acromegaly rather than in gigantism.
- Teeth
 - Increased tooth size especially root due to secondary cemental hyperplasia.
 - Diastema between teeth due to lengthening of dental arch.
- Jaw bone
 - In acromegaly, the angle between the ramus and body of the mandible may increase, which results in an anterior tooth root push forward so they appear as fan out.
 - Enlargement of the mandible, the length of the horizontal and ascending rami are both increased.
 - Enlargement of inferior dental canal is seen.

Management

- Surgery: Transsphenoidal surgery may result in the cure of GH excess, especially in patients with macroadenoma.
- Medical therapy: Octreotide, a long-acting analogue of somatostatin, lowers GH. It is administered as subcutaneous insulin 2–3 times daily. Dopamine antagonists are also used.
- Radiotherapy: External radiotherapy stops tumour growth and lowers GH levels. GH levels fall slowly and there is a risk of hypopituitarism.

Hypopituitarism

Pituitary is the master gland of the body. The reduced secretion of pituitary hormone may result in pituitary dwarfism. Total absence of all pituitary secretions is known as *panhypopituitarism*. Hypopituitarism which commences after puberty is called as *Simmond's disease.*

Causes

- Congenital or due to destructive disease of pituitary gland such as infarct occurring before puberty.
- Lesions involving the sella turcica like craniopharyngioma, adenomas and sarcoidosis.
- *Sheehan's syndrome* is a form of hypopituitarism caused by infarction of the pituitary associated with postpartum haemorrhage.

Clinical features

- Stature: The underdevelopment is symmetrical, individual is very small and in some cases there may be a disproportional shortening of the long bones.
- Hypocalcaemia: It may occur because of growth hormone and cortisol deficiency. Lack of gonadotrophin delays the onset of puberty.
- Diabetic insipidus: The presence of diabetes insipidus associated with deficient secretion of vasopressin is suggestive of pituitary dysfunction.
- Growth hormone secretion is lost resulting in lethargy, muscle weakness and increase fat mass in adults.
- Impaired luteinizing hormone (LH) secretion shows loss of libido and impotence in males and oligomenorrhoea or amenorrhoea in females.
- The skull and facial bones show delayed union and maturation.

Oral manifestations

- Jaw bone: Underdevelopment of maxilla and mandible with lack of condylar growth with short ramus and this can lead to severe malocclusion and crowding of the teeth.
- Teeth: The two important hormones excreted by this gland—the somatotrophic and the thyrotrophic, are responsible for the normal eruption of teeth and the alveolar growth. Thus, in case of hypofunction of this gland, the tooth eruption is impaired. The dental arch is smaller than normal and thus cannot accommodate all the teeth resulting in crowding and subsequent malocclusion.

Radiographic features

- Teeth: Complete absence of third molars. Roots of teeth are short and apices are wide open.
- Alveolar bone: There is loss of alveolar bone.

Management

It is usually directed towards removal of the cause or replacement of the pituitary hormone or those of its target glands.

Diseases of thyroid gland

Hyperthyroidism

It is also called as *thyrotoxicosis* and is a syndrome in which there is excessive production of thyroxin in thyroid gland. It is associated with diffuse toxic goitre and less frequently with toxic nodular goitre or toxic adenoma. Excessive thyroxin causes generalized increase in metabolic rate of all body tissues. In patient with thyrotoxicosis, dental treatment can precipitate an acute emergency like *thyroid crisis* or *thyroid storm*.

Causes

- Exophthalmic goitre: It is characterized by diffuse hyperplasia of the thyroid and eye signs.
- Toxic adenoma: Hyperfunction originates by a benign tumour of the thyroid gland.
- Ectopic thyroid tissue, Graves' disease, multinodular goitre, thyroid adenoma.

Clinical features

- Thyroid appears diffusely enlarged, smooth, possible asymmetrical and nodular appearance. A thrill and tenderness may be present.
- Neuromuscular: Nervousness, fine tremors, muscle weakness, euphoria, emotional liability, hyperreflexia, ill-sustained clonus, proximal myopathy, bulbar myopathy and periodic paralysis.
- Gastrointestinal: Weight loss despite of normal or increased appetite, diarrhoea, bowel alterations, anorexia, vomiting and hyperdefecation. Abdomen, liver and spleen may be enlarged.
- Cardiorespiratory: Palpitation, excessive perspiration, irregular heart beat will be present. Increased metabolic activity leads to increased circulatory demands, tachycardia and increased pulse pressure and sometimes congestive cardiac failure.
- Ocular: Patient may have bulging eye and partial paralysis of the ocular muscles, retraction and jerky movement, corneal ulceration, optic neuritis, ocular muscle weakness, papilloedema, loss of visual activity and exophthalmos.
- Reproductive: Amenorrhoea, oligomenorrhoea, infertility, spontaneous abortion and loss of libido, impotence.

- Dermatological: Increased sweating, pruritus, oncolysis, pigmentation, vitiligo, digital clubbing and pretibial myxoedema (bilateral nonpitting oedema).
- Others: Heat intolerance, sweaty and warm extremities, thin shiny skin, pretibial myxoedema, early fatigue, lymphadenopathy, thirst and osteoporosis.

Oral manifestations

- Teeth: Advanced rate of dental development and early eruption with premature loss of primary teeth.
- Alveolar bone: Generalized decrease in bone density or loss of some areas of edentulous alveolar bone.

Radiographic features

- In older children and adults, well-marked generalized osteoporosis appears but it is not revealed in the jaw.
- In some cases, there may be alveolar resorption and in few cases there may be greater density of the trabeculae.

Management

- General: Sedate the patient giving medication. Application of cold packs to lower the body temperature.
- Antithyroid drugs: Carbimazole for 0 to 3 weeks—40 to 60 mg daily in divided doses; for 4 to 8 weeks—20 to 40 mg daily in divided doses and for maintenance phase—5 to 20 mg daily.
- Subtotal thyroidectomy.
- Radioactive iodine-131 (^{131}I): It acts either by destroying functioning thyroid cells or by inhibiting their ability to replicate. Dose—185 to 370 mEq is given orally.

Hypothyroidism

It is an insufficient secretion of thyroxin by the thyroid gland. Failure of thyrotrophic function on the part of the pituitary gland or an atrophy or destruction of the thyroid gland leads to an inability of the thyroid to produce sufficient hormone to meet the requirement of the body.

Causes

Thyroiditis, insufficient thyroid replacement, post-thyroidectomy, postradioactive iodine therapy.

Types

- Cretinism: It occurs due to deficiency of hormone during infancy.
- Juvenile myxoedema: It occurs due to deficiency of hormone during childhood.
- Myxoedema: Deficiency occurs after the puberty.

Clinical features

Cretinism and juvenile myxoedema

- Age. It may be present at birth or become evident within the first few months after birth.
- Symptoms: Hoarse cry, constipation, feeding problems in neonates, retarded mental and physical growth.
- Bones: Delayed fusion of all body epiphysis and delayed ossification of paranasal sinus.
- Signs: The hairs are sparse and brittle, the finger nails are brittle and the sweat glands are atrophic.

Myxoedema

- **Symptoms**
 - Early symptoms: It may include weakness, fatigue, cold intolerance, lethargy, dryness of skin, headache, menorrhagia and anorexia.
 - Late symptoms: It includes absence of sweating, modest weight gain, constipation, peripheral oedema, pallor, hoarseness, decreased sense of taste and smell, muscle cramps, aches and pains, dyspnoea, anginal pain and deafness.
- **Signs**
 - Dull expressionless face, periorbital oedema, sparse hair and skin that feels droughty to touch.
 - Facial pallor, puffiness of face and eyelids (myxoedema), occasional purpura, thickened nose and lips in more advanced cases are seen.
 - Thyroid gland may be enlarged, thin brittle nails, coarse thin hair, dry rough skin, displaced apical beat may be present.

Oral manifestations

Cretinism and juvenile myxoedema

- Teeth
 - Delayed tooth development and primary teeth exfoliation.
 - Enamel hypoplasia can also be seen.
 - Abnormalities of dentine formation lead to enlarged pulp chamber.
- Jaw bone: Retarded condylar growth leads to characteristic mandibular micrognathia and open-bite relationship.
- Tongue: Tongue is enlarged due to accumulation of oedema fluid.
- Skull: The base of skull is shortened leading to a retraction of the bridge of the nose with flaring.
- Face: Brachycephaly.
- Lips are puffy, thickened and protruding.

Myxoedema

- Tongue and lip: Macroglossia and enlarged lip as a result of the deposition of fluid and protein.
- Face: Facial swelling of non-pitting type and mandible is underdeveloped.
- Teeth: There is greater tendency to periodontal disease, with alveolar destruction and loosening of the teeth.

Radiographic features

- Skull bones: Delayed closing of the fontanels and epiphysis, numerous wormian bones (accessory bone in the sutures).
- Teeth
 - Thinning of lamina dura.
 - Delayed dental eruption and short tooth root.
 - Separation of teeth as a result of enlargement of tongue, periodontal diseases and loss of teeth, and external root resorption.

Complications

- Coronary artery disease, congestive heart failure.
- Increased susceptibility to infection, mental disturbances including depression.

Management

Thyroid preparation: Levothyroxine is available as 25, 50 and 100 mg tablets. It is customary to start slowly and a dose of 50 mg daily should be given for 3

weeks and finally to 150 mg daily.

Dental consideration of thyroid disorders

- In dentistry, the use of sedatives and analgesics is dangerous, as these agents tend to precipitate coma in the patients with hypothyroidism.
- Supporting respiration.
- Circulation narcotic antagonist may be given.
- In patients with severe hyperthyroidism, the emergencies likely to occur are thyroid crisis, emotional disturbances and cardiac difficulties.
- Treatment by the dentist should consist of medication to sedate the patient, application of cold packs to lower body temperature.
- If severe, the patient should be immediately hospitalized.

Diseases of parathyroid gland

- Parathyroid glands are four small glands which produce and release parathormone, which maintains plasma ionized calcium level.
- Ionized calcium is essential for:
 - Bone and tooth development
 - Neuromuscular excitability
 - Membrane fluidity
 - Membrane integrity
 - Cell communication
 - Cell adhesion
 - Blood clotting
- Two well-known manifestations associated with parathyroid gland are:
 1. Hyperparathyroidism: which affects primarily on bones and the kidneys
 2. Hypoparathyroidism: Tetany

Hyperparathyroidism

(Synonym: Osteitis fibrosa cystica)

- Hyperparathyroidism is a disease in which the parathyroid glands elaborate an excessive quantity of parathyroid hormones.
- This increased activity is usually due to:
 - Adenoma of one or more of the four parathyroid glands
 - Hyperplasia of the parathyroid tissue
 - Carcinoma of parathyroid gland
- Excess parathyroid hormone (PTH) stimulates osteoclast to mobilize calcium from skeleton leading to hypercalcaemia and also PTH increases renal tubular reabsorption of calcium.
- Hypercalcaemia may be seen by poor muscle tone and decreased neuromuscular excitability.

Clinical features

- **Age.** 30–60 years of age.
- **Sex.** Female predilection.
- **Symptoms**
 - Renal calculi, haematuria, back pain, urinary tract infection and hypertension are common.
 - Peptic ulcer, psychiatric effect like emotional instability, bone and joint

pain, and sometime pathologic fractures occur.
- Gastrointestinal difficulties such as anorexia, nausea, vomiting and crampy pain may be present.
- Bone: Bone deformities occur such as bending of long bone, occasional fracture and collapse of vertebrae, and formation of pigeon chest.
- Hypercalcaemia: It is associated with muscle weakness, fatigue, weight loss, insomnia, headache, polydipsia and polyuria.

Oral manifestations

- Teeth: Gradual loosening, drifting and loss of teeth and malocclusion.
- Jaw bone: Sometimes, pathological fracture of bone is seen. Cystic lesion involving jaws are seen over 10% of cases.

Radiographic features

- Demineralization of skeleton: Bone matrix contains less amount of calcium producing unusual radiolucent skeletal image. There is lack of normal contrast in the radiograph resulting in overall greyness, often associated with a granular appearance in the bone.
- Ground glass appearance: The rarefaction is of homogenous nature and there may be normal, granular or ground glass appearance.
- Moth-eaten appearance: Sometimes rarefaction gives a mottled or moth-eaten appearance with varying density.
- Osteitis fibrosa generalisata: Localized destruction of bone is produced by osteoclastic activity leaving residual area of fibrosis.
- Pathological calcification: Punctuate and nodular calcifications occasionally occur in kidneys and joints.
- Skull bones: Entire calvarium has granular appearance caused by loss of central trabeculae and thinning of cortical plates.
- Pepper-pot skull: Osteopaenia producing a fine overall stippled pattern to the skull bone, hence it is called as pepper-pot skull.
- Jaw bones: Demineralization of inferior border of mandibular canal, thinning of outlines of the maxillary sinus is seen.
- Teeth and alveolar bone
 - If the alveolus is severely affected, the teeth may become mobile and migrate.
 - Loss of lamina dura may be seen around single or multiple teeth. It may be complete or partial.

Brown tumour

- It is named so because the gross specimen appears brown or reddish brown in colour.
- It may develop peripherally or centrally.
- It appears radiographically as ill-defined radiolucency and trabeculae are rarely seen.
- It may occur in pelvis, ribs or femur but are most commonly found in facial bones and jaws.
- These lesions may be multiple within the single bone or they may be polyostotic.
- These appear as unilocular or multilocular with variably defined margins and may produce cortical expansion.

Histopathological features

- There is osteoclastic resorption of the trabeculae of the spongiosa and along the blood vessels in the haversian system of the cortex.
- Fibrosis especially in the marrow spaces is marked.
- Resorbed trabeculae are replaced by dense fibrotic islands, recent and old haemorrhage with much haemosiderin.
- Large tortuous blood-filled sinusoidal channels are lined by a flat endothelial layer.
- Multinucleated giant cells lie adjacent to the sinusoids and osteoid trabeculae tend to orient themselves in close proximity to the vascular spaces.

Management

- It often regresses without surgery and the rarefaction disappears.
- Surgical excision of adenoma.
- The oral administration of vitamin D in secondary type can prevent skeletal demineralization in most of the cases.

Hypoparathyroidism

- It is caused by a group of heterogenous conditions in which hypocalcaemia and hyperphosphataemia occurs as a result of deficient parathyroid hormone secretion.
- Calcium levels in extracellular tissues are normally regulated by PTH in conjunction with vitamin D. If calcium levels drop below a certain point

then the release of PTH is stimulated. The hormone then acts directly on the kidney and the osteoclasts of bone to restore the calcium to normal levels.

- In kidney, calcium reabsorption is promoted, phosphate excretion is enhanced and the production of vitamin D is stimulated, which increases the absorption of calcium from gut. The osteoclasts are activated to resorb bone and thus liberate calcium.

Different forms of hypoparathyroidism are as follows:

1. **Isolated**
 a. *Autosomal dominant*
 - Prepro PTH signal peptide mutation
 - CASR activating mutation

 b. *Autosomal recessive*
 - Prepro PTH RNA splice-site mutation
 - GCM-2 mutation

 c. *X-linked*
2. **Congenital multisystem syndromes**
 a. DiGeorge and velocardiofacial syndromes
 b. Barakat syndrome
 c. Kenny–Caffey syndrome
3. **Metabolic disease**
 a. Mitochondrial neuromyopathies
 b. Long chain hydroxyl acyl-CoA dehydrogenase
 c. Heavy metal storage disorders
4. **Autoimmune disease:** Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome—endocrine candidiasis syndrome
5. **Pseudohypoparathyroidism**

Clinical features

- Neuromuscular hyperexcitability due to hypocalcaemia. The effect may be aggravated by hyperkalaemia or hypomagnesaemia.
- Patient may complain of circumoral numbness, paraesthesia of distal extremities or muscle cramping which can progress to carpopedal spasm or tetany.
- Laryngospasm or bronchospasm and seizures may also occur.
- Other manifestations include fatigue, irritability and personality disturbances.

- Chvostek's sign: It is characterized by a twitching of the upper lip, when the facial nerve is tapped just below the zygomatic process. A positive response suggests a latent degree of tetany.
- Patients with chronic hypocalcaemia may have calcification of the basal ganglia or more widespread intracranial calcification detected by skull X-ray or CT scan.
- If hypoparathyroidism develops early in life during odontogenesis then a pitting enamel hypoplasia and failure of tooth eruption may occur.

Management

- Supplemental calcium and vitamin D depending on severity of the hypocalcaemia and the nature of associated signs and symptoms.
- In severe cases, intravenous administration of calcium gluconate is the treatment of choice.

Diseases of pancreatic gland

Diabetes mellitus

- It is a common endocrine disorder characterized by chronic hyperglycaemia and abnormalities in carbohydrate and lipid mechanism.
- Diabetes mellitus (DM) is an inappropriate hyperglycaemia due to tissue resistance to insulin action, reduced insulin secretion or both.

Aetiology

- It is caused by disorders of carbohydrate mechanism resulting from insulin deficiency or ineffectiveness, producing hyperglycaemia and glycosuria.
- Genetic, autoimmune and pancreatic dysfunctions.

Types

1. **Primary**
 - Type I or insulin-dependent diabetes mellitus (IDDM): It occurs due to deficiency of insulin.
 - Type II or noninsulin-dependent diabetes mellitus (NIDDM): It occurs due to insulin resistance.
 - Non-obese
 - Obese
 - Maturity onset diabetes of the young (MODY)
2. **Secondary**
 - Pancreatic disease (pancreatitis, haemochromatosis, neoplastic disease, pancreatectomy, cystic fibrosis).
 - Endocrine disease: Excess endogenous production of hormonal antagonists to insulin, e.g. growth hormone in acromegaly.
 - Drug-induced like corticosteroid, thiazide diuretics and phenytoin.
 - Genetic syndrome like Down syndrome, Klinefelter's syndrome and Turner's syndrome.

Causes

Type I diabetes mellitus

- Viruses: Several viruses are implicated including infection with mumps coxsackie B, retrovirus, rubeolla and cytomegalovirus and Epstein–Barr

virus. Virus particles known to cause cytopathic or autoimmune damage to beta cells of pancreas.

- Diet: Bovine serum albumin (BSA), a major constituent of cow's milk has been implicated in triggering type I diabetes. It has been shown that a child who has taken cow's milk early in infancy has been more prone to develop type I diabetes mellitus as compared to others who have taken breast milk.
- Stress: It may precipitate the development of type I diabetes by stimulating the secretion of counter-regulatory hormones and possibly by modulating immune activity.
- Immunological factors: There is evidence that type I diabetes is a T cell mediated autoimmune disease. There is also HLA linked genetic predisposition. Monocular cell infiltration of pancreatic islets restoration in selective destruction of insulin secreting cells and induction of remission by immunosuppressive drugs such as cyclosporine suggest an immunological aetiology.

Type II diabetes mellitus

- Genetic: The majority of causes of type II diabetes are multifactorial. Various types are associated with it like hepatocyte nuclear factor, glucokinase and mitochondrial DNA and insulin receptors.
- Environmental factors
 - Lifestyle: Overeating, especially when combined with obesity and under-activity is associated with development of type II diabetes.
 - Malnutrition: It is proposed that malnutrition in utero and the infancy may damage beta cells and predispose to type II diabetes later in life.
 - Age: Age is an important risk factor for type II diabetes as it is principally disease of middle aged population.
 - Pregnancy: During normal pregnancy, insulin sensitivity is reduced through the action of placental hormone and this affects glucose tolerance. The term *gestational diabetes* refers to hyperglycaemia occurring for the first time during pregnancy.
- Insulin resistance occurs in type II diabetes is due to an abnormal insulin molecule, an excessive amount of circulating antagonists and target tissue defect.

Clinical features

- Polydipsia: There is excessive intake of fluid.

- Polyuria: There is excessive urine passage.
- Polyphagia: There is excessive hunger.
- Breathe: There is presence of acetone breathe.
- Visual activity: Visual difficulty ranging from progressive colour blindness to total blindness.
- Atherosclerosis: Coronary artery disease and stroke are frequent complications.
- Diabetic neuropathy: It can cause marked irritability.
- Infection: Recurrent vaginal infections, recurrent urinary tract infections, recurrent skin infections (especially of feet) and reversible paraesthesia of fingers or toe.
- Other symptoms
 - Nocturia, weight loss, fatigue, obesity usually present in older age group, nausea, vomiting.
 - Temperature, blood pressure may be elevated and peripheral pulses may be reduced.

Oral manifestations

- Gingival and periodontal disease
 - It will influence the onset and course of periodontal disease. Patients with diabetes are more prone to develop periodontal disease.
 - The patient may exhibit a fulminating periodontitis and periodontal abscess.
 - Teeth mobility is frequently seen.
 - Severe and rapid alveolar bone resorption is seen.
 - Insulin-dependent diabetic children tend to have more destruction around the first molars and incisors than elsewhere.
 - As such diabetes mellitus does not cause periodontal disease directly, but it alters the response of the periodontal lesion to local irritants, hastening bone loss and retarding post-surgical healing of the periodontal lesions.
 - Gingival fluid in the diabetes has more glucose level which favours the growth of microflora.
- Oral candidiasis: It occurs due to encouragement of local multiplication of *Candida albicans* due to impaired glucose level and immune mechanism.
- Localized osteitis: Dry socket develops frequently in diabetes due to delayed healing and impaired immunological balance.
- Diabetes is often associated with a variety of unexplained oral symptoms

such as burning sensation, atypical paresis, dysarthria and dysgeusia.

- Trigeminal nerve involvement: Diabetes neuropathy is recognized as a polymorphic condition manifested as polyneuropathy. Trigeminal nerve is commonly involved.
- Other features
 - Increased caries activity: Due to excessive fluid loss, the patient complains of xerostomia.
 - There is also atrophy of lingual papillae with fissuring and dry tongue.
 - There is delay in healing of oral wound due to decreased polymorphonuclear chemotaxis.
 - There are also angular cheilosis, altered taste sensation, oral lichen planus and diffuse enlargement of parotid gland.

Radiographic features

- Slight discontinuity or blurring of the cortex of alveolar crest to wide destruction of lamina dura is seen.
- Horizontal and vertical bone loss of alveolar bone is seen.

Management

- Diet control.
- Oral hypoglycaemic drugs: If dietary management proves ineffective in controlling hyperglycaemia, hypoglycaemic drugs like insulin or oral hypoglycaemics are prescribed.
- Sulphonylurea: First generation sulphonylurea—tolbutamide is given in a dosage of 25 or 500 mg 8 or 12 hourly. Second generation sulphonylurea—gliclazide and glipizide are widely used.
- Metformin in a dose of 500 mg 12 hourly is commonly used. Its use is contraindicated in persons with impaired renal or hepatic function and in those who take alcohol in excess because of risk of lactic acidosis.
- Insulin therapy: Insulin was discovered in 1921. The duration of action of short-acting unmodified insulin can be extended by addition of protamine and zinc at neural pH. Insulin is injected subcutaneously into recommended sites like anterior abdominal wall, upper arms, outer thighs and buttocks. Insulin has to be injected at least 30 minutes before a meal to allow adequate time for absorption. Side effects of insulin are hypoglycaemia, weight gain, peripheral oedema, insulin antibodies, local allergy and lipodystrophy.

Complications

- Ketoacidosis, coronary artery disease and peripheral vascular disease.
- Recurrent skin and urinary infections, renal and retinal changes and cataracts.
- Peripheral neuropathy, premature mortality and hyperosmotic nonketotic coma.

Diabetes insipidus

Causes

- It occurs due to insufficiency of the posterior pituitary hormone.
- Traumatic episodes, such as head trauma or surgical procedures carried out near the pituitary region, can often lead to destruction of the posterior lobe of the pituitary.
- There will be damage to the neurohypophyseal mechanism for the production of vasopressin.
- Posterior pituitary disorders like craniopharyngioma and basal meningitis.

Clinical features

- Increased thirst and passage of large quantities of urine. Urine of low specific gravity.
- Dehydration, headache, irritability and fatigue may occur due to restriction of fluid.

Management

- Administration of vasopressin is the treatment of choice. Desmopressin can be given intranasally in a dose of 5–10 mg once or twice daily.

Diseases of adrenal gland

Addison's disease

It is also known as *chronic adrenal insufficiency* of the adrenal cortex. It was first described by Addison in 1855.

Causes

- Autoimmune: Sporadic and polyglandular syndrome.
- Tuberculosis, metastatic carcinoma, intradermal haemorrhage, amyloidosis, haemochromatosis, adrenal infarction and congenital adrenal hypoplasia.
- Drugs like aminoglutethimide, ketoconazole and etomidate.

Clinical features

- **Age.** 30–40 years.
- **Sex.** Male predilection.
- **Symptoms.** Feeble heart action, general debility, vomiting, diarrhoea and severe anaemia. Patient may complain of postural hypotension.
- **Sign.** The disease is characterized by bronzing of skin, a pigmentation of the mucous membrane.
- Metabolic function: The decreased cortisol level interferes with the production of carbohydrates from protein causing hypoglycemia and diminished glycogen storage in the liver.
- Neuromuscular function is inhibited producing muscle weakness.
- There is also reduced resistance to infection, trauma and stress.

Oral manifestation

The pale brown or deep chocolate pigmentation of the oral mucosa, spreading over the buccal mucosa from the angle of the mouth and/or developing on the gingiva, tongue, lips may be the first evidence of disease.

Histopathological features

Biopsy of oral lesion shows acanthosis with silver positive granules in the cells of the stratum germinativum.

Management

Glucocorticoids replacement: Cortisol is the drug of choice. In patients who

are not critically ill, hydrocortisone 15 mg is given in the morning and 5 mg in the evening.

Cushing's syndrome

Cushing's syndrome arises from excess secretion of glucocorticoids by the adrenal glands. It was described by Harvey Cushing in 1932.

Causes

- Adrenal adenoma, adrenal carcinoma, adrenal hyperplasia and basophilic adenoma of the anterior lobe of pituitary gland.
- Exogenous corticosteroid.
- Ectopically located adrenal tumour like in ovary.
- Alcohol excess, major depressive illness and primary obesity.

Clinical features

- **Age.** 30–40 years.
- **Sex.** Males.
- Moon face: Rapidly acquired obesity about upper portion of the body and rounded moon face are seen.
- Buffalo hump: There is truncal obesity with prominent supraclavicular and dorsal cervical fat pads giving rise to the 'buffalo hump' appearance at the base of neck.
- Other features: The distal extremities are usually thin. Weakness, hypertension, or concurrent diabetes is usually present.
- Hair: Sparse and brittle hair is seen.
- Abdomen: Dusky plethoric appearance with formation of purple striae on abdomen is seen.
- Weight loss, menstrual irregularity, hirsutism, backache, obesity, hypertension can also occur.

Oral manifestations

- In children, growth and development including skeletal and dental age may be retarded.
- In some instances, there may be osteoporosis of the jaws.

Radiographic features

- Generalized osteoporosis is present. The bones likely to involve are the vertebrae and the ribs although the long bones may be affected.

- Skull: It may show diffuse thinning and mottled appearance.
- Lamina dura: Jaw may show areas of loss of lamina dura.

Management

- If the lesion in the pituitary gland is the cause, therapy usually consists of a combination of surgery and radiotherapy.
- Drugs: Metyrapone, 2–6 g per day in divided doses is advised. Aminoglutethimide, an anticonvulsant drug, blocks steroid synthesis.
- Radiotherapy: In adrenocortical hyperplasia, irradiation is the best treatment.
- Surgery: Tumours involving the adrenal cortex are removed surgically and often require postoperative administration of corticosteroids to maintain normal glucocorticosteroid level.

Key points

- The normal serum calcium level is 9–11 mg/dl.
- *Calcium deficiency:* Hyperirritability, carpopedal spasm, laryngospasm and convulsions.
- *Phosphorus deficiency:* Weakness, malaise, anorexia and bone pain.
- *Dystrophic calcification:* Calcium salts deposit in dead or degenerating tissues.
- *Metastatic calcification:* Calcium salts precipitate due to high level of blood calcium.
- *Sodium deficiency:* Gradual weakness, excessive fatigue, lassitude, apathy, anorexia, nausea, muscle cramps and peripheral vascular collapse.
- *Potassium deficiency:* Death due to cardiac or respiratory failure, muscular irritability, muscular weakness, reduced or absent reflexes, mental confusion, paralysis.
- *Amyloidosis:* Abnormal proteinaceous substance (*amyloid*) deposition in tissues and organs of the body.
- *Mucopolysaccharidoses:* Abnormal deposition of glycosaminoglycans in tissues and organs of the body.
- *Hurler syndrome:* The excessive intracellular accumulation of both chondroitin sulphate B and heparin sulphate in tissues and organs of the body.
- *Hand–Schuller–Christian disease:* Both skeletal system and soft tissues are involved.

- *Eosinophilic granuloma:* Only bone is affected and soft tissues are rarely involved.
- *Letterer-Siwe disease:* It is an acute fulminating disease with involvement of both skeletal and extraskeletal tissues including the skin.
- *Gaucher's disease:* Deposition of glucocerebroside in cells of macrophage–monocyte system.
- *Niemann–Pick disease:* Accumulation of sphingomyelin in cells due to deficiency of sphingomyelinase.
- *Thiamine (vitamin B_1) deficiency:* Beriberi, Wernicke's encephalopathy, peripheral neuritis and Korsakoff's psychosis.
- *Riboflavin (vitamin B_2) deficiency:* Dermatitis, photophobia, interstitial keratosis, dull or oily skin, premature wrinkles on face, brittle nails, glossitis and cheilitis.
- *Niacin (vitamin B_3) deficiency:* Pellagra.
- Pantothenic acid (vitamin B_5) *deficiency:* Muscle cramps, mental depression, irritability, dizziness, gastric distress and constipation.
- *Pyridoxine (vitamin B_6) deficiency:* Peripheral neuropathy, mental retardation, irritability, mental confusion, nervousness, glossitis and cheilitis.
- *Biotin (vitamin B_8) deficiency:* Scaly dermatitis, eczema, seborrhoea, confusion, mental depression, muscular weakness, extreme fatigue and lassitude.
- *Folic acid (vitamin B_9) deficiency:* Anaemia, skin pigmentation, spontaneous abortions, dementia, mental depression, fatigue, severe glossitis, cheilitis and ulcerative stomatitis.
- *Cyanocobalamin (vitamin B_{12}) deficiency:* Megaloblastic anaemia or pernicious anaemia, Hunter's glossitis, generalized weakness, numbness and tingling sensation of extremities, fatigue, headache, dizziness, nausea, vomiting and diarrhoea.
- *Vitamin C deficiency:* Scurvy.
- *Vitamin A (retinol) deficiency:* Night blindness, Bitot's spot, keratomalacia, xerophthalmia, xerostomia, keratinizing metaplasia, sterility, pimples, acne, premature wrinkles, hypoplasia of teeth, delayed or cessation of eruption.
- *Vitamin D deficiency:* Rickets and osteomalacia.
- *Vitamin E (tocopherol) deficiency:* Sterility, degenerative changes in muscles and blood capillaries, pulmonary embolism and brain stroke.

- *Vitamin K (phylloquinone) deficiency:* Prolongation of clotting time.
- *Hyperpituitarism:* Gigantism and acromegaly.
- *Hypopituitarism:* Pituitary dwarfism.
- *Hyperthyroidism:* Thyrotoxicosis, thyroid crisis, early eruption and premature loss of primary teeth.
- *Hypothyroidism:* Cretinism and juvenile myxoedema.
- *Hyperparathyroidism*: Affects bones and the kidneys.
- *Hypoparathyroidism:* Tetany.
- *Type I or insulin-dependent diabetes mellitus:* Deficiency of insulin.
- *Type II or noninsulin-dependent diabetes mellitus:* Insulin resistance.
- *Diabetic insipidus:* Deficiency of the posterior pituitary hormone.
- *Addison's disease:* Chronic adrenal insufficiency of the adrenal cortex.
- *Cushing's syndrome:* Excess secretion of glucocorticoids by the adrenal glands.

Frequently asked questions

1. Discuss the disturbances in mineral metabolism.
2. Pathological calcifications.
3. Discuss the disturbances in carbohydrate metabolism.
4. Hurler syndrome.
5. Hand–Schuller–Christian disease/eosinophilic granuloma/Letterer–Siwe disease/Gaucher's disease/Niemann–Pick disease.
6. Water-soluble vitamin deficiency.
7. Beriberi.
8. Vitamin B_{12} deficiency.
9. Scurvy.
10. Vitamin K deficiency.
11. Acromegaly.
12. Hyperparathyroidism.
13. Brown tumour.
14. Oral manifestations in diabetes mellitus.

CHAPTER 15

Allergic and immunologic diseases

Allergy is a broad term used generally to describe the hypersensitive state of the immune system, acquired by exposure to specific material (antigen) and the altered capacity of the living organism to react upon re-exposure to the antigen.

Recurrent aphthous stomatitis

(Synonym: Canker sores)

- It is a common disease characterized by the development of painful recurring solitary or multiple ulcerations of the oral mucosa.
- Areas of ulceration on the mucous membranes are termed as *aphthous.*

Pathogenesis

The exact aetiology is unknown, but various other causes have been proposed as follows:

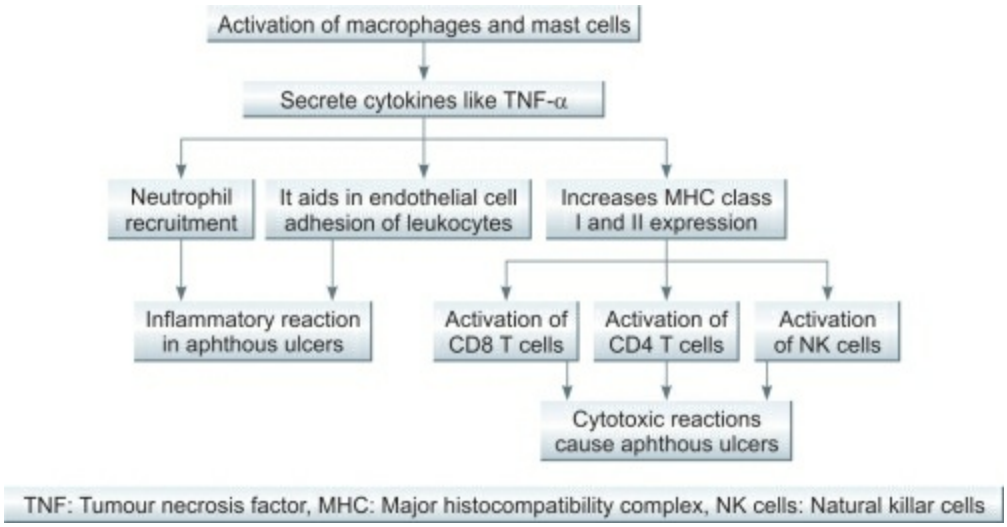
- Psychological—stress, anxiety, depression, etc.
- Immunologic disorders
- Neurogenic inflammation—neuropeptide induced, e.g. substance P
- Mucosal healing defect—inhibition by cytokines
- Microbiologic factors—bacterial (α-haemolytic streptococcus, *S. sanguis*), viral (herpes simplex virus, varicella-zoster virus, cytomegalovirus)
- Nutritional deficiency—vitamin B_{12}, folic acid, iron

Precipitating factors

- **Local factors**
 - Tobacco smoking
 - Trauma
 - Dentifrices
- **Systemic factors**
 - Behcet's disease
 - Sweet's syndrome
 - Cyclic neutropenia
 - Allergic factors: Drugs, e.g. NSAIDs
 - Inflammatory bowel disease

Cell-mediated immunity

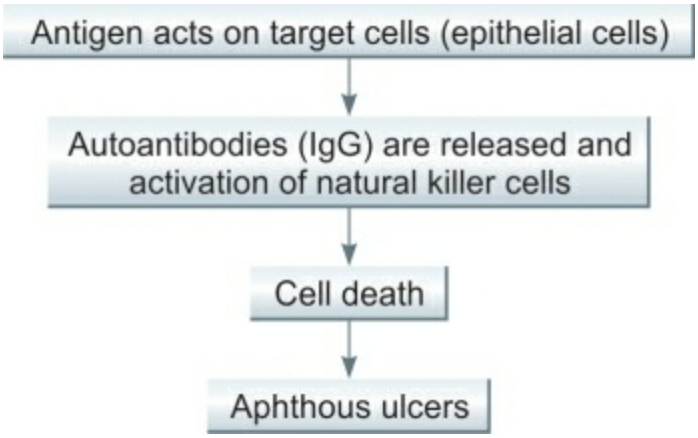
Flowchart 15.1 depicts the cell-mediated immunity of recurrent aphthous stomatitis.



FLOWCHART 15.1 Pathogenesis of aphthous ulcer (cell-mediated immunity)

Humoral-mediated immunity

Flowchart 15.2 depicts the humoral-mediated immunity of recurrent aphthous stomatitis.



FLOWCHART 15.2 Pathogenesis of aphthous ulcer (humoral-mediated immunity)

Classification

Based on clinical manifestations

- Recurrent aphthous minor (canker sore)—the most common form
- Recurrent aphthous major (Mikulicz's scarring aphthae or Sutton's disease)—the most severe form
- Recurrent herpetiform ulcerations
- Recurrent ulcers associated with Behcet's syndrome

Clinical features

Recurrent aphthous minor

- **Age.** 10–30 years.
- **Gender.** Female predilection.
- **Site.** Nonkeratinized mucosa, e.g. lips, cheeks, tongue, soft palate and fauces.
- The frequency of occurrence varies from person to person. Few individuals will have only one or two attacks a year, while others will have one or two attacks a month and almost every month for prolonged periods, sometimes years.
- The aphthous ulcer begins as a single or multiple superficial erosions covered by a grey membrane with clearly defined, raised margins surrounded by an erythematous halo.
- The lesion is typically painful, so it commonly interferes while eating and speaking for several days.
- The ulcers themselves generally persist for 7–14 days and then heal gradually with little or no evidence of scarring.
- Recurrence is common.

Recurrent aphthous major

- **Age.** 10–30 years.
- **Gender.** Female predilection.
- **Site.** Nonkeratinized mucosa is commonly involved.
- It is characterized by the occurrence of large painful ulcers usually 1 to 10 in number and cause severe pain and dysphagia.
- It occurs more commonly among HIV patients.
- These ulcers occur at frequent intervals.
- They reach a large size, usually about 1 cm in diameter or even larger.
- The ulcers may exceed 1 cm in diameter and persist for up to 6 weeks and leave a scar upon healing, which leads to restricted mouth opening.

- Recurrence is common.

Recurrent herpetiform ulcers (herpeti–herpes; form–like)

- **Age.** 10–30 years.
- **Gender.** Female predilection.
- **Site.** They involve any part of oral cavity, including the keratinized mucosa.
- **Size and number.** Initially, multiple small ulcers which increase in size, and coalesce to leave large round ragged ulcers. They are larger in number, even greater than 100.
- These are often extremely painful.
- Lesions are present almost continuously for 1–3 years with relatively short remissions.

Histopathology

- It is characteristic but not pathognomonic.
- *Ulcer* is defined as a discontinuity of epithelium with exposure of underlying connective tissue.
- The surface of the ulcer is covered by a fibrinous exudate infiltrated by polymorphs.
- Beneath is a layer of granulation tissue with dilated capillaries and oedema.
- *Anitschkow cells* (Fig. 15.1) are epithelial cells with elongated nuclei containing a linear bar of chromatin with radiating processes of chromatin extending towards the nuclear membrane. The appearance of these cells is characteristic but not pathognomonic. It is also a feature of sickle cell, megaloblastic and iron-deficiency anaemias.
- Diagnosis of aphthous is based on exclusion of other ulcerated lesions.

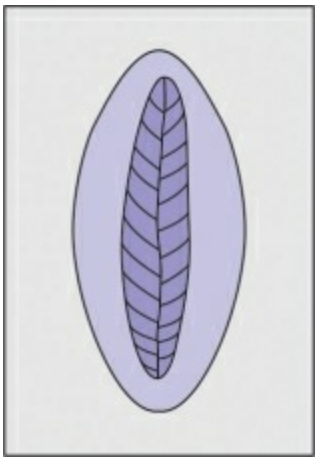


FIG. 15.1 Anitschkow cell.

Differential diagnosis

- Herpetic ulcers
- Traumatic ulcers
- Pemphigus vulgaris

Prognosis and predictive factors

- There is no specific treatment to be instituted.
- Symptomatic treatment to reduce pain and recurrence of lesion is advised.
- Tetracycline mouthwash four times daily for 5–7 days will produce a good response.

Table 15.1 describes comparison of aphthous ulcers and herpes simplex ulcers.

Table 15.1

Comparison of aphthous ulcers and herpes simplex ulcers

Features	Aphthous ulcer	Herpes infection
Pathogenesis	Immune dysfunction	HSV-1
Triggers	Stress, trauma, diet, hormones, depressed immunity	Stress, trauma, ultraviolet light, depressed immunity
Appearance	Little prodrome Nonspecific microscopic features No vesicles Single, oval ulcer	Prodromal symptoms Viral cytopathic changes Vesicles precede ulcers Multiple, confluent ulcers
Sites	Nonkeratinized mucosa	Keratinized mucosa
Treatment	Corticosteroids, tetracyclines	Antiviral treatment

Table 15.2 describes comparison of minor aphthae, major aphthae and

herpetiform aphthae.

Table 15.2

Comparison of minor aphthae, major aphthae and herpetiform aphthae

Features	Minor aphthae	Major aphthae	Herpetiform aphthae
Size	<0.5 cm	>0.5 cm	<0.5 cm
Shape	Oval	Ragged oval, crateriform	Oval
Number	1–5	1–10	10–100
Location	Nonkeratinized mucosa	Nonkeratinized mucosa	Any intraoral

Behcet's syndrome

(Synonym: Adamantiades syndrome)

- Earlier this disorder was considered to affect only oral, genital and ocular regions.
- Now it is considered as multisystem disorder involving visceral organs such as the gastrointestinal tract, pulmonary system, musculoskeletal and neurological system too.

Pathogenesis

- The primary aetiology is not well known.
- It is considered to be immunogenetic because of the association with specific HLA (human leukocyte antigen) types.
- The immunodysregulation may have several triggering factors such as bacterial and viral infections, pesticides and heavy metals.
- The immunologic competence and cytotoxic potential of lymphocytes to oral mucosa suggest that these cells might cause the epithelial damage, which results in ulceration. Cytokines and heat shock proteins are considered to be major factors in the pathogenesis of Behcet's syndrome.

Clinical features

- **Age.** 30–40 years.
- **Gender.** Male predilection.
- **Location.** Oral, genital and ocular mucosa.

- **Signs and symptoms.** It is characterized by oral and genital ulcerations, ocular lesions and skin lesions:
 - Oral involvement: Oral lesions are painful and very similar clinically and histologically to that of recurrent aphthous ulcers. They occur in crops and ranging in size from several millimetres to centimetres or more in diameter. It occurs at any intraoral site. These ulcers have an erythematous border and are covered by grey or yellow exudates. Differences with aphthous ulcers include:
 - Number: More lesions (>6).
 - Site: Involvement of soft palate and oropharynx is also seen.
 - More deeper and associated with ragged borders.
 - Less recurrence rate.
 - Genital lesions: Similar in appearance to the oral ulcerations. These lesions recur less frequently than oral ulcerations. They are deeper and tend to heal with scarring.
 - Cutaneous lesions: They include erythematous papules, vesicles, pustules, pyoderma, folliculitis, acneiform eruptions and erythema nodosum-like lesions.
 - Ocular involvement: Hypopyon (pus in the anterior chamber) as a cause of blindness. Secondary ocular complications are cataracts, glaucoma and neovascularization of iris and retina.
 - Arthritis: Common minor manifestations of the disease and is usually self-limiting and non-deforming. The knees, wrists, elbows and ankles are affected.
 - CNS involvement: Paralysis and severe dementia may occur.
 - Other alterations may be seen that involve CVS, GIT, haematologic, pulmonary, muscular and renal system.

Histopathology

- It is not pathognomonic.
- The pattern most frequently seen is called *leukocytoclastic vasculitis.*
- The ulceration is similar to aphthous stomatitis, but the small blood vessels classically demonstrate intramural invasion by neutrophils, karyorrhexis of neutrophils, extravasation of RBCs and fibrinoid necrosis of the vessel wall.

Prognosis and predictive factors

- There is no specific treatment for the disease other than symptomatic or

supportive measures.
- Behcet's disease may undergo spontaneous remission after a variable period of months to years.
- Sometimes, it may progress to serious complications and even result in death due to complicated rupture of vascular aneurysms or severe neurological complications.

Reiter's syndrome

It is associated with urethritis, balanitis, conjunctivitis and mucocutaneous lesions.

Pathogenesis

- The exact aetiology is unknown, although there is evidence of an infectious origin. Pleuropneumonia-like organisms (PPLO), mycoplasmal and chlamydial species are isolated.
- This disease may be triggered by infectious agents in genetically susceptible patients.
- HLA-B27 is considered to be a disease susceptibility factor.
- This disease is also seen usually in HIV-positive patients.

Clinical features

- **Age.** 20–40 years.
- **Gender.** Male predilection.
- **Location.** Oral, genital and ocular mucosa.
- **Signs and symptoms.** There is tetrad of manifestations:
 - Non-gonococcal urethritis
 - Arthritis
 - Conjunctivitis
 - Mucocutaneous lesions
- Urethritis is first sign and is seen in both males and females. The urethral discharge is usually associated with itching and burning sensation.
- The arthritis usually affects the joints of lower extremities, although temporomandibular joint involvement is also seen with erosions of condylar head.
- Conjunctivitis is often mild as to be overlooked.
- The skin lesions are similar to keratoderma blennorrhagica and consist of red or yellow keratotic macules or papules which eventually desquamate.

- Oral lesions appear as painless, red, slightly elevated areas sometimes granular or even vesicular with a white circinate border on the buccal mucosa, lips and gingiva.
- Clinically, similar lesions occur on the glans penis producing a circinate balanitis.

Histopathology

- It is not diagnostic.
- It consists of parakeratosis, acanthosis and polymorphonuclear leukocyte infiltration of epithelium, sometimes with microabscess formation similar to psoriasis and elongated, thin rete ridges.
- The connective tissue shows lymphocyte and plasma cell infiltrate.

Prognosis and predictive factors

The disease may undergo spontaneous remission but has been treated by antibiotics and corticosteroids.

Sarcoidosis

(Synonyms: Boeck's sarcoid; Besnier–Boeck–Schaumann disease)
Sarcoidosis is described as a multisystem granulomatous disease of unknown origin characterized by the formation of uniform, discrete, compact, non-caseating epithelioid granulomas.

Pathogenesis

- The exact aetiology is not known.
- The possible involved antigens include:
 - Infectious agents: *Mycobacterium*, Epstein–Barr virus, human herpes virus-8.
 - Environmental factors: Wood, dust, pollen, clay, mould, silica.
- The improper degranulation of antigenic material with formation of non-caseating granulomatous inflammation.
- The inappropriate defence response may result from prolonged or heavy antigenic exposure, an immunodysregulation (genetic or secondary to other factors) that prevents an adequate cell-mediated response, a defective regulation of the initial immune reaction or a combination of all three of these factors.

- Prolonged antigenaemia, circulating immune complexes and serum inhibitors contribute to the granulomatous disorder.
- Interferon gamma (IFN-γ) and cytokines such as TNF-α, IL-12 and IL-18 play an important role in the formation of granulomatous lesions.

Clinical features

- **Age.** Bimodal age distribution, first peak: 25–35 years and second peak: 45–65 years.
- **Gender.** Female predilection.
- **Location.** Lungs, lymph nodes, skin, eyes and salivary glands.
- **Signs and symptoms**
 - The clinical symptoms include dyspnoea, dry cough, chest pain, fever, malaise, fatigue, arthralgia and weight loss.
 - 20% of patients have no symptoms and the disease is discovered in routine chest radiographs.
 - *Cutaneous manifestations*
 - Chronic, violaceous, indurated lesions—*lupus pernio* occurs on nose, ears, lips and face.
 - Symmetrical, elevated, indurated, purplish plaques are seen commonly on limbs, back and buttocks.
 - Scattered, nonspecific, tender erythematous nodules known as *erythema nodosum,* frequently occur on lower legs.
 - *Ocular involvement*
 - Anterior uveitis, and lesions on conjunctiva and retina may occur.
 - Lacrimal glands involvement—keratoconjunctivitis sicca
 - *Salivary gland involvement*
 - Enlargement of major and minor salivary glands
 - Xerostomia
 - Two distinctive clinical syndromes are associated with acute sarcoidosis
 - *Lofgren's syndrome:* It consists of erythema nodosum, bilateral hilar lymphadenopathy and arthralgia.
 - *Heerfordt's syndrome:* Parotid enlargement, anterior uveitis of the eye, facial paralysis and fever.
 - *Oral manifestations*
 - Site: Buccal mucosa, gingiva, lips, floor of the mouth, tongue and palate.
 - It appears as a submucosal mass, an isolated papule, an area of granularity or ulceration.

- The mucosal lesions may be normal in colour, brownish-red or violaceous and hyperkeratotic in appearance.
- Lesions on lip appear small papular nodules or plaques.
- Lesions on palate and buccal mucosa appear bleb-like containing yellow fluid or as solid nodules.
- Intraosseous lesions show ill-defined radiolucencies that occasionally eroded with cortex but never created expansion.

Histopathology

- It exhibits a non-caseating granulomatous inflammation.
- Tightly clustered aggregates of epithelioid histiocytes are present with a surrounding rim of lymphocytes and intermixed with Langhans or foreign body giant cells.
- The granulomas often contain laminated basophilic calcifications known as *Schaumann bodies* (degenerated lysosomes) or stellate inclusions known as *asteroid bodies* (entrapped fragments of collagen).
- In lymph nodes, small yellow brown structures called *Hamazaki–Wesenberg bodies* (large lysosomes) may be seen in subcapsular sinus.
- Caseation and necrosis do not occur, although granuloma ultimately transforms into solid, amorphous, eosinophilic, hyaline mass as it ages.

Diagnosis

- The tuberculin reaction will be positive.
- An intracutaneous test for the diagnosis of sarcoidosis, the *Kveim–Siltzbach test*, has been devised, utilizing a suspension of human known sarcoidal tissue as the test agent. It is a high degree of specificity test. It is an important aid in the early and accurate diagnosis of the disease.

Prognosis and predictive factors

- In most of the cases, the symptoms resolve spontaneously within 2 years without treatment.
- Corticosteroids remain first-line therapy, but resistance and relapse are common.
- Medications used in patients with refractory disease include methotrexate, azathioprine, chlorambucil and cyclophosphamide.
- Antimalarial medications such as chloroquine have demonstrated effectiveness in resolving mucocutaneous sarcoidosis that was resistant to

steroids.
- Approximately, 4–10% of patients die of pulmonary, cardiac or CNS complications.

Wegener's granulomatosis

- It is an uncommon granulomatous disease.
- It is a necrotizing granulomatous lesion of the respiratory tract, necrotizing glomerulonephritis and systemic vasculitis of small arteries and veins.

Pathogenesis

- Exact aetiology is unknown.
- It is an abnormal immune reaction secondary to a nonspecific infection or an aberrant immune reaction to an inhaled antigen or infection.
- It also is believed to be a hereditary lesion.

Clinical features

- **Age.** Any age group.
- **Gender.** No sex predilection.
- **Location.** It can involve all organ systems of the body.
- **Signs and symptoms**
 - *Classic Wegener's granulomatosis*: Initially show involvement of upper and lower respiratory tracts, if untreated then renal involvement often rapidly develops—*generalized granulomatosis.*
 - *Limited Wegener's granulomatosis:* Involvement of respiratory system without rapid development of renal lesions.
 - *Superficial Wegener's granulomatosis:* Lesions primarily involve skin and mucosa. Systemic involvement develops slowly.
 - *Upper respiratory tract involvement:* It shows purulent nasal drainage, chronic sinus pain, nasal congestion, fever, dry cough, dyspnoea, chest pain and haemoptysis with progression, destruction of nasal septum (saddle nose deformity).
 - *Lower respiratory tract involvement:* Asymptomatic. Patient may have dry cough, haemoptysis, dyspnoea and chest pain.
 - *Renal involvement:* Glomerulonephritis results in proteinuria and RBC casts, which may lead to death.
 - *Oral manifestations*

- They are uncommon, but sometimes oral lesions may be the initial presentation.
- Gingivitis: Florid and granular hyperplasia is seen.
- Surface forms numerous short bulbous projections, which are haemorrhagic and febrile, strawberry-like appearance, *strawberry gingivitis.*
- Buccal surface of gingiva is mostly affected, first interdental surface is involved, then it extends laterally to involve adjacent areas.
- It may be localized or generalized to involve multiple quadrants.
- Destruction of underlying bone with development of tooth mobility has been reported.
- Nonspecific ulcerations can occur in the oral cavity.

- Facial paralysis, labial mucosal nodules, arthralgia of TMJ, jaw claudication, palatal ulceration from nasal extension, oroantral fistula and poor healing extraction sites may also occur.

Histopathology

- Epithelium may show pseudoepitheliomatous hyperplasia and subepithelial abscess.
- Involved vessels demonstrate transmural inflammation with areas of heavy neutrophilic infiltration, necrosis and nuclear dust *(leukocytoclastic vasculitis).*
- Connective tissue adjacent to vessels has an inflammatory cell infiltrate which contains mixture of histiocytes, lymphocytes, eosinophils and multinucleate giant cells.

Prognosis and predictive factors

- Disease can be fatal in few months to few years, if not treated.
- Corticosteroids, cyclophosphamide, methotrexate, cyclosporine, trimethoprim-sulphamethoxazole, etc. are advised.

Angioedema

(Synonyms: Angioneurotic oedema; Quincke's disease)

- Angioedema is a diffuse oedematous swelling of the soft tissues that most commonly involves the subcutaneous and submucosal connective tissues but may affect the gastrointestinal or respiratory tract, occasionally with fatal results.

- The disorder has been referred to as *Quincke's disease,* after the clinician who initially related the changes to an alteration in vascular permeability —Quincke (1882).
- Angioneurotic oedema is named because affected patient often complains of a choking sensation and is labelled neurotic. Also many patients present with psychological problems.

Pathogenesis

The commonly observed causes of angioedema are as follows:

- *Allergic angioedema (due to mast cell degranulation):* Mast cell degranulation leads to histamine release and the typical clinical manifestations. It is seen commonly in IgE-mediated hypersensitivity reactions caused by drugs, foods, plants, dust, and inhalants, contact allergic reactions to foods, cosmetics, topical medications, and even dental rubber dams. Mast cell degranulation can also result from physical stimuli such as heat, cold, physical exercise, emotional stress and solar exposure.
- *Associated with use of angiotensin-converting enzyme (ACE) inhibitors:* It is related to the use of ACE inhibitors, commonly used in the treatment of hypertension. These drugs cause angioedema by increasing the levels of bradykinin. This form of angioedema usually arises within hours of initial use of the drug.
- *Activation of the complement pathway*
 - *Hereditary form:* Two rare autosomal dominant hereditary forms are seen.
 1. Type 1 is caused by a quantitative reduction in the inhibitor that prevents the transformation of C1 to C1 esterase. Without adequate levels of this inhibitor (C1-INH), C1 esterase cleaves C4 and C2 and results in angioedema.
 2. Type 2 exhibits normal levels of C1-INH, but the inhibitor is non-functional.
 - *Acquired form:* It is seen in association with certain type of lymphoproliferative diseases in patients who develop specific antibodies. The lymphoid proliferation increases the consumption of C1-INH and the autoantibodies prevent the binding of C1-INH to C1.

Clinical features

- **Age.** Puberty, rarely in children.
- **Gender.** No sex predilection.

- **Location.** Face around the lips, chin, eyes, tongue, pharynx and larynx. Sometimes hands, arms, legs, genitals and buttocks.
- **Signs and symptoms**
 - Angioedema manifests as a soft, non-tender, diffuse oedematous swelling of relatively rapid onset, which may be solitary or multiple in number.
 - Involvement of the skin and mucous membrane can cause enlargements that can measure up to several centimetres in diameter.
 - The eyes may be swollen and shut.
 - The lips will be extremely puffy.
 - A feeling of tenseness or an itching or prickly sensation sometimes precedes the urticarial swelling.
 - The skin may be of normal colour or slightly pink.
 - Perioral and periorbital oedemas are characteristic features.
 - The enlargement usually resolves within 24–72 hours, although some cases persist for several days.
 - Involvement of the upper airway can be life-threatening.
 - Hoarseness of voice and difficulty in breathing are important signs.
 - Gastrointestinal symptoms include continuous pain, vomiting and rarely watery diarrhoea.

Prognosis and predictive factors

- When the aetiologic agent such as food can be discovered, its elimination from the diet will prevent recurrent attacks.
- The oedema can be treated by antihistaminic drugs.
- If the attack is not controlled or if laryngeal involvement is present, intramuscular epinephrine should be administered.
- If epinephrine does not stop the attack, intravenous corticosteroids and antihistamines should be given.

Key points

- *Recurrent aphthous stomatitis* is a common disease characterized by the development of painful recurring solitary or multiple ulcerations of the oral mucosa.
- *Anitschkow cells:* Recurrent aphthous stomatitis, sickle cell, megaloblastic and iron-deficiency anaemia.
- *Behcet's syndrome* is a multisystem disorder involving visceral organs.

- *Reiter's syndrome:* Urethritis, balanitis, conjunctivitis and mucocutaneous lesions.
- *Sarcoidosis* is a multisystem granulomatous disease of unknown origin characterized by the formation of uniform, discrete, compact, non-caseating epithelioid granulomas.
- *Lofgren's syndrome:* Erythema nodosum, bilateral hilar lymphadenopathy and arthralgia.
- *Heerfordt's syndrome:* Parotid enlargement, anterior uveitis of the eye, facial paralysis and fever.
- *Midline lethal granuloma* is an idiopathic progressive destruction lesion of the nose, paranasal sinuses, palate, face and pharynx.
- *Wegener's granulomatosis* is a necrotizing granulomatous lesion of respiratory tract, necrotizing glomerulonephritis and systemic vasculitis of small arteries and veins.
- *Angioedema* is a diffuse oedematous swelling of the soft tissues that most commonly involves the subcutaneous and submucosal connective tissues but may affect the gastrointestinal or respiratory tract, occasionally results in death.

Frequently asked questions

1. Discuss pathogenesis, clinical features and histopathology of recurrent aphthous stomatitis.
2. Behcet's syndrome.
3. Sarcoidosis.
4. Wegener's granulomatosis.
5. Angioedema.

CHAPTER 16

Diseases of the bones and joints

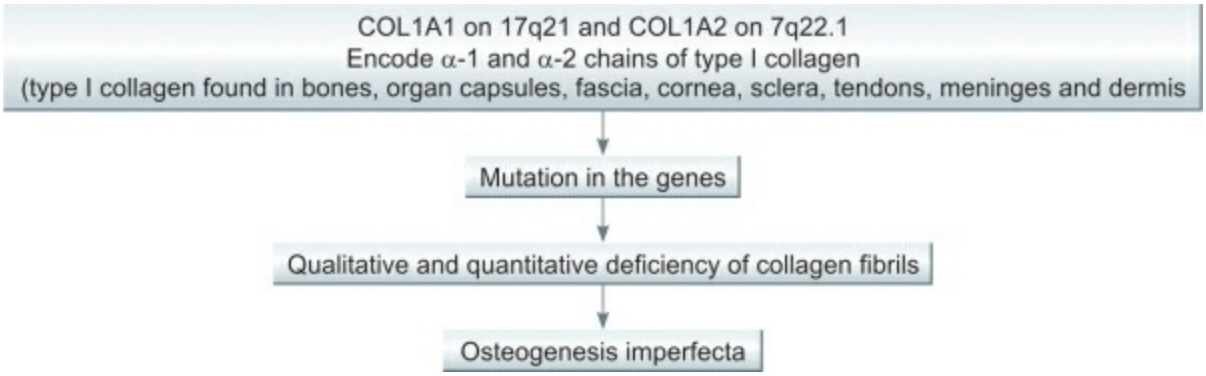
Osteogenesis imperfecta

(Synonyms: Brittle bone disease; Lobstein's disease)

- Osteogenesis imperfecta (OI) is a group of inherited diseases responsible for varying degrees of skeletal fragility. Minimal trauma is sufficient to cause fractures and bone deformities.
- Usually transmitted as an autosomal dominant trait and characterized by abnormality in type-I collagen which commonly manifests as fragility of bone.

Pathogenesis

Flowchart 16.1 describes pathogenesis of osteogenesis imperfecta.



FLOWCHART 16.1 Pathogenesis of osteogenesis imperfecta

Clinical features

- Extreme fragility of bones with increased proneness to fracture.
- Fractures heal readily but the new bone formed is of imperfect quality.
- Prenatal ultrasound in second trimester shows bowing of long bones, fractures and limb shortening.
- Sclera is thin and pigmented; choroid shows through and produces bluish colour.

Note: Blue sclera is also seen in osteopetrosis, fetal rickets, Paget's disease, Marfan's syndrome, Turner's syndrome and Ehlers–Danlos syndrome.

- Deafness due to osteosclerosis.
- Laxity of ligaments and capillary bleeding.

Classification

Silence et al in 1979 classified osteogenesis imperfecta into seven different types:

Type-I (osteogenesis imperfecta tarda): Mild form

- Common and mildest form.
- Slender weak tendons and pale blue sclera.
- Gene map locus: 17q21.3-q22; 7q22.1.
- Two subtypes:
 1. Type-A: Dentinogenesis imperfecta is absent.
 2. Type-B: Dentinogenesis imperfecta is present.
- Mild to moderate bone fragility.
- Kyphoscoliosis.
- Hearing loss and bruising.

Type-II: Lethal form

- Extreme bone fragility
- Intrauterine fractures in 100% of cases.
- Stillbirth and 90% die before 4 weeks of age.
- Blue sclera.
- Dentinogenesis imperfecta, small nose, micrognathia and short trunk.

Type-III: Severely progressive

- It is associated with dentinogenesis imperfecta (DI) and blue-yellow, small misshapen teeth, which are formed secondary to the type-I collagen defect.
- Limb shortening and progressive deformities.
- Frontal bossing and triangular facies.
- Intrauterine fractures in more than 50% of cases and remaining half of the cases have fractures in neonatal period.

Type-IV: Moderately severe form

- Usually, it is differentiated from *type-I* by having normal sclera and *type-III by* autosomal dominant inheritance.
- Two subtypes:
 1. Type-A: DI is absent.
 2. Type-B: DI is present.
- Hearing loss and fractures begin in the infancy.
- Bleeding diathesis.

Type-V: Mild to moderate severe form

- Mild to moderately severe OI, which does not appear to be associated with collagen type-I mutations.
- Normal coloured sclera and ligament laxity.
- DI will not be present.
- Typically, patients have ossification of interosseous membrane of the forearm with radial head dislocation, hyperplastic callus formation and an abnormal histopathological pattern.

Type-VI: Moderate to severe form

- Moderate to severe form of disease with accumulation of osteoid due to a mineralization defect, in the absence of a disturbance of mineral metabolism.
- More frequent fractures than any other type of OI.
- Fractures are first documented between 4 and 18 months of age.
- Sclerae are white or faintly blue and DI is uniformly absent.
- All patients have vertebral compression fractures.
- The underlying genetic defect is not yet known.

Type-VII: Moderate to severe form

- Recessive form.
- Fractures at birth, bluish sclera, early deformity of the lower extremities and osteopaenia.
- Rhizomelia (proximal limb shortening) is a prominent clinical feature.
- The disease has been localized to chromosome 3p22–24.1.

Oral manifestations

- Large forehead, frontal and temporal bossing
- Anterior and posterior crossbite

- Maxillary hypoplasia
- Large number of impactions
- Ectopic teeth
- Unerupted permanent first and second molars

Radiographic features

Osteopaenia, bowing, angulation and deformity of long bones, multiple fractures and wormian bones are seen.

Histopathology

- It exhibits thin cortices with immature spongy bone.
- Trabeculae of bone are delicate and show microfractures.
- Osteoblastic activity is impaired.
- Failure of fetal collagen to transform into mature collagen.
- Qualitative and quantitative defects in collagen exist, cross-linking of collagen essential for normal maturation is absent.
- Teeth show abnormalities of dentine similar to dentinogenesis imperfecta.

Differential diagnosis

- Achondrogenesis.
- Nonaccidental injury is the main differential diagnosis in childhood.
- During late childhood and adolescence, idiopathic juvenile osteoporosis.

Prognosis and predictive factors

- There is no cure for OI.
- OI is the leading cause of lethal short-limbed dwarfism and crippling skeletal dysplasia.
- Treatment is directed towards preventing or controlling the symptoms, maximizing independent mobility, and developing optimal bone mass and muscle strength.

Marfan syndrome

(Synonym: Arachnodactyly)

- It is an inherited defect of connective tissue that has autosomal mode of transmission.
- Marfan syndrome is named after Antoine Marfan, the French

paediatrician, who first described the condition in 1896.
- People with this syndrome are tall and thin with long fingers and arm bones, and have an arm span that exceeds their height.

Pathogenesis

- Defect in FBN1 gene located on 15q15–23, which encodes for a glycoprotein called *fibrillin-1*, a component of extracellular matrix.
- The fibrillin-1 protein is essential for the proper formation of the extracellular matrix including the formation and maintenance of elastic fibres.

Clinical features

- No sex predilection
- Long slender limbs with long fingers and toes (arachnodactyly)
- Aortic aneurysms
- Kyphosis and scoliosis
- Shape of skull is long and narrow
- Hyperextensibility of joints
- Mitral valve prolapse
- Pigeon chest deformity
- Myopia, retinal detachment and superior dislocation of joints

Oral manifestations

- Long and narrow face
- High-arched palate
- Cleft palate
- Bifid uvula
- Malocclusion
- TMJ dysarthrosis

Prognosis and predictive factors

- There is no cure.
- Orthodontic treatment for malocclusion and corrective surgery for cleft palate.

Achondrogenesis

- Achondrogenesis is a heterogenous group of lethal disorders that is characterized by a severe form of congenital chondrodysplasia in humans.
- It causes death in intrauterine life or in early neonatal life.

Types

- **Type-1:** *Subtypes*
 - *Type-1A:* Houston–Harris achondrogenesis
 - *Type-1B:* Fraccaro achondrogenesis
- **Type-2:** Langer–Saldino achondrogenesis

Pathogenesis

- *Type-1A:* It is of an autosomal recessive inheritance with an unknown chromosomal locus.
- *Type-1B:* It is an autosomal recessive disorder resulting from mutations in *DDST* (diastrophic dysplasia sulphate transporter) gene, which is located at 5q32–q33.
- *Type-2* is an autosomal dominant type collagenopathy resulting from mutations in *COL2A1* (collagen 2α1 chain) gene, which is located at 12q13.1-q13.3.

Clinical features

- No sex predilection.
- Achondrogenesis is detected prenatally or at birth because of typical clinical, radiographic, histopathological and molecular findings.
- Type-1 achondrogenesis results in stillbirth and it occurs more frequently than type-2.
- *Type-1 achondrogenesis:* Craniofacial features include a disproportionately large head, soft skull, sloping forehead, convex facial plane, flat nasal bridge, deep horizontal groove, small nose, anteverted nostrils, long philtrum, retrognathia, increased distance between lower lip and lower edge of chin and double chin appearance.
- *Type-2 achondrogenesis:* Disproportionately large head, large and prominent forehead, flat facial plane, flat nasal bridge, small nose with severe anteverted nostrils, normal philtrum and micrognathia.

Histopathology

- **Type-1A**

- Normal cartilage matrix
- No collagen rings are present around chondrocytes
- Vacuolated chondrocytes
- Intrachondrocytic inclusion bodies (PAS positive and diastase resistant)
- Enlarged lacunae
- Woven bone

- **Type-1B:** Cartilage matrix shows coarse collagen fibres that are particularly dense around chondrocytes forming collagen ring.
- **Type-2**
 - Slightly larger than normal and grossly distorted (lobulated and mushroomed) epiphyseal cartilage.
 - Severe disturbances in endochondral ossification and hypercellular reserve cartilage with large, primitive mesenchymal (ballooned chondrocytes with abundant clear cytoplasm).
 - Cartilaginous matrix is markedly deficient.

Prognosis and predictive factors

- There is no cure.
- Genetic counselling and antenatal diagnosis help in prevention.

Osteopetrosis

(Synonyms: Marble bone disease; Albers-Schonberg disease)

- A German radiologist, Albers-Schonberg, first described osteopetrosis in 1904.
- Osteopetrosis is a group of rare hereditary skeletal disorders characterized by a marked increase in bone density resulting from a defect in remodelling caused by failure of normal osteoclasts function.
- The defect in bone turnover characteristically results in skeletal fragility despite increased bone mass, and it may also cause haematopoietic insufficiency, disturbed tooth eruption, nerve entrapment syndromes, and growth impairment.

Pathogenesis

- Failure of osteoclastic bone resorption results in increased bone mass.
- Thickened sclerotic bones have poor mechanical properties.
- Mutations underlying osteopetrosis interfere in relation to process of acidification of osteoclast resorption pit.

- Autosomal recessive defect of gene results in carbonic anhydrase-2 (CA2) deficiency.
- CA2 is required by osteoclasts to generate CO_2 and H_2O.
- Absence of CA2 prevents osteoclasts from acidifying resorption pits.
- Mutations in chloride channel gene (CLCN7), proton pump gene and RANKL gene may result in altered osteoclastic activity.

Clinical features

Three types of clinical patterns of osteopetrosis are detected:
1. Infantile osteopetrosis: Autosomal recessive
2. Intermediate osteopetrosis: Autosomal recessive
3. Adult osteopetrosis: Autosomal dominant

Infantile osteopetrosis (malignant osteopetrosis)

- Diagnosed early in life, growth retardation and failure to survive.
- Nasal stuffiness due to mastoid or paranasal sinus malformation.
- Cranial nerve entrapment and neuropathies due to failure of foramina to widen completely.
- Deafness, proptosis and hydrocephalus, delayed eruption of teeth.
- Osteomyelitis of mandible, defective osseous tissue replaces bone marrow which results in pancytopenia, anaemia, bleeding and recurrent infections.
- Increased susceptibility to infection is common as a result of granulocytopenia.
- Extramedullary haematopoiesis, hepatosplenomegaly and haemolysis.

Intermediate osteopetrosis

- Recessively inherited bone disease characterized by brittle bones with increased density.
- Less severe than the infantile form but more severe than the adult form.
- Nerve compression, hepatosplenomegaly and pancytopenia.

Adult osteopetrosis (benign osteopetrosis)

- Diagnosed in adolescence and adulthood.
- Most of the patients are asymptomatic.
- Patients may present with osteomyelitis or fractures.
- Bone pain, cranial nerve entrapment, neuropathies, carpal tunnel syndrome and osteoarthritis.

- Osteomyelitis, visual impairment, short stature, frontal bossing, nystagmus, hepatosplenomegaly.

Oral manifestations

- Medullary spaces are reduced in both dominant and recessive osteopetrosis.
- Development of osteomyelitis of jaws is seen.
- Fracture of jaws during extraction is common because of bone fragility.
- Teeth are of defective quality, enamel hypoplasia, dentinal defects and arrested root development.
- Retardation of tooth eruption due to sclerosis of bone.

Radiographic features

- Bones are uniformly sclerotic, club-like and show an appearance of bone within bone *(endo-bone)*.
- Entire skull is thickened.
- Sinuses are small and under pneumatized.
- Vertebrae are radiodense and show alternating bands known as *rugger jersey sign*.
- Radiographs may show fractures.

Histopathology

- Failure of osteoclasts to resorb skeletal tissue is the pathognomonic feature of true osteopetrosis.
- Endosteal production of bone with apparent concomitant loss of physiologic bone resorption is seen.
- Osteoblasts are prominent but osteoclasts are seldom found.
- Trabeculae show disorderly arrangement and marrow tissue is usually fibrous.
- Adult patients with benign osteopetrosis appear to have deficiency in osteoclastic activity.

Prognosis and predictive factors

- Gamma interferon therapy.
- Vitamin D substitutes.
- Corticosteroids.
- Bone marrow transplantation in cases of infantile osteopetrosis.

- Adult osteopetrosis requires no treatment by itself, although complications of the disease require intervention.

Osteoporosis

It is characterized by porous bone and reduced bone mass.

Pathogenesis

- *Primary:* Post-menopausal, senile, idiopathic.
- *Secondary:* Endocrine disorders, e.g. hyperparathyroidism, hyperthyroidism, hypothyroidism, hypogonadism, pituitary tumours, diabetes type-1, Addison's disease.
- *Neoplasia:* Multiple myeloma, carcinoma.
- *GIT:* Malnutrition, malabsorption, hepatic insufficiency, vitamins C and D deficiencies.
- *Drugs:* Anticoagulants, chemotherapy, corticosteroids, anticonvulsants and alcohol.
- *Miscellaneous:* Osteogenesis imperfecta, immobilization, anaemia.

Predisposing factors

- Age-related changes in bone cells and matrix have strong impact on bone metabolism; osteoblasts of elderly people have reduced biosynthetic potential.
- Reduced physical activity.
- Genetic factors: Genes like RANKL, OPG are involved.
- Nutritional status.
- Hormonal influences, after menopause → decreased oestrogen → increased secretion of inflammatory cytokines → bone resorption.

Clinical features

- It manifests commonly in women after menopause.
- Fatigue and pain of weight-bearing joints affect their function.
- Vertebral fractures of thoracic and lumbar region.
- Kyphoscoliosis.
- Lumbar reaction.
- Remains asymptomatic until fragility is advanced.

Prognosis and predictive factors

Exercise, calcium and vitamin D intake and bisphosphates.

Paget's disease

(Synonym: Osteitis deformans)

- The disease is named after Sir James Paget, who first reported it in 1876.
- The term *osteitis deformans* is now considered technically incorrect and the preferred term is *osteodystrophia deformans.* It was called *osteitis deformans* as it was believed that the disease was caused by chronic inflammation.
- The disease is marked by repeated episodes of increased bone resorption followed by excessive attempts at repair, resulting in weakened, deformed bones of increased mass. The resultant architecture of the bone assumes a mosaic pattern in which the fibres take on a haphazard pattern instead of the normal parallel symmetry.

Pathogenesis

- Exact cause is unknown.
- *Genetics:* The recurrent mutations in the sequestosome 1 gene (SQSTM 1) (also known as p62), which participates in the regulation of osteoclastic activity via the nuclear factor-κB (NF-κB) transcription activation pathway, have been identified in both familial and sporadic cases of the disease. Mutations in other genes, *valosin-containing protein (VCP)* gene, involved in NF-κB signalling pathway, have been found in patients with a rare hereditary syndrome that includes Paget's disease of bone, body myopathy and frontotemporal dementia.
- *Viral infection:* Virus infection may be necessary to trigger Paget's disease in people who have inherited the genetic tendency to develop the condition by having these genes. Paramyxoviral inclusion particles are observed in osteoclasts as well as increased viral antibody titres.
- *Inflammatory cause:* The presence of inflammatory cells in bone and peripheral blood. Clinical improvement after treatment with anti-inflammatory medications.
- *Others:* Elevated parathyroid hormone, autoimmune, connective tissue and vascular disorders are proposed as other possible aetiologies.

Clinical features

- Majority of patients are asymptomatic and diagnosis is made incidentally during radiographic or biochemical investigations.

- Age: >50 years.
- Sex: No sex predilection.
- Location: Lumbar vertebrae, pelvis, skull and femur.
- Paget's disease may affect one bone and then remain limited in its course (monostotic) or progress from a few localized areas to the rest of the skeleton (polyostotic).
- Musculoskeletal impairments with neurologic and cardiovascular complications.
- The most common complaint is bone pain—dull aching, constant pain, involved bones become warm to touch due to increased vascularity.
- Other features:
 - Pathologic fractures due to weakened pagetic bone
 - Nonspecific headaches
 - Deafness, blindness, hearing loss due to nerve compressions
 - Impaired healing
 - Tinnitus
 - Cranial nerve palsies
 - Platybasia: Softened bone at base of the skull may lead to discrete of cranium on to cervical spine, progressive pain, paraesthesia, limb paresis, waddling gait, bowel and bladder incontinence.

Oral manifestations

- Maxilla: mandible—2:1.
- Leontiasis ossea.
- Nasal obstruction.
- Enlarged turbinates.
- Obliterated sinuses.
- Deviated septum.
- Maxilla shows progressive enlargement, alveolar ridge becomes widened and palate will be flattened.
- If teeth are present, they become loose, migrate and produce spacing.
- Inability to wear dentures.

Radiographic features

- The destructive lesions may be multiple or isolated.
- The large radiolucent lesion in the skull is described as *osteoporosis circumscripta*.
- Osteoblastic phase is easily recognized as it appears as opacities in

radiograph, which are patchy in distribution. This patchiness is called *cotton-wool appearance*.

- A significant finding is loss of normal trabeculation.
- Generalized hypercementosis, loss of lamina dura and root resorption are seen.

Histopathology (fig. 16.1)

- Paget's disease consists of three phases:
 1. Initial osteolytic stage
 2. Mixed osteoblastic and lytic change
 3. Osteoclastic change
- Osteolytic phase is marked by disordered areas of resorption by an increased number of large osteoclasts. Osteoclasts may contain as many as 100 nuclei.
- Osteoblastic phase is characterized by haphazard deposition of new bone.
- Multiple reversal lines are seen due to repeated bone removal and formation giving an appearance of *jigsaw puzzle* or *mosaic bone pattern*. The reversal lines are deeply haematoxyphilic and are a histologic hallmark of Paget's disease.
- As the disease progresses, osteoblastic phase predominates causing more compact and dense bone. The pagetic bone is coarse and fibrous with avidity for calcium and phosphorus.
- Marrow spaces are filled with loose highly vascularized connective tissue. Increased vascularity consists of increased number of patent capillaries, dilated arterioles and larger venous sinuses.
- Pagetic bone shows no tendency to form haversian system or to centre on blood vessels; the bones are very hard and dense.
- Eventually, the osteoblastic activity diminishes and an osteoporotic or burned-out phase predominates.

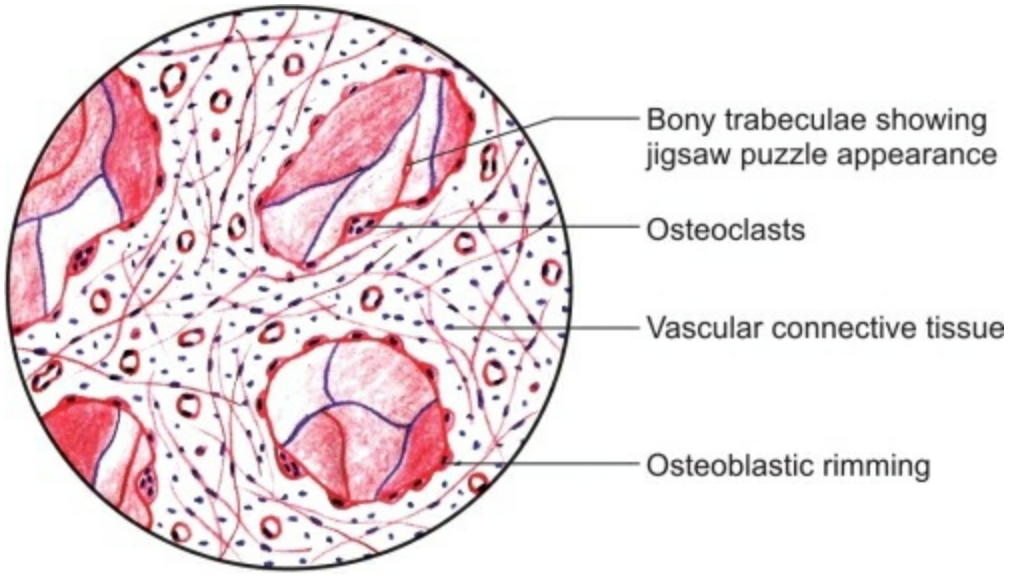


FIG. 16.1 Paget's disease.

Laboratory findings

- Increased alkaline phosphatase: 250 Bodansky units, particularly in osteoblastic phase of disease and polyostotic involvement. In monostotic involvement, serum alkaline phosphatase level will be 50 Bodansky units.
- Urinary hydroxyproline level is increased, suggesting an increased osteoclastic activity (hydroxyproline is a product of collagen breakdown).
- Urinary excretion of bone specific pyridinium collagen crosses links, N-telopeptide, alpha-C-telopeptide: Sensitive and specific index of bone resorption.

Prognosis and predictive factors

- Bisphosphonates
- Calcitonin
- Surgical correction for bone deformities, fractures and severe degenerative arthritis
- **Complications**
 - *Fractures*
 - Incomplete stress fractures are seen in weakened pagetic bones
 - Pathologic fractures are more common
 - Site: Femur, tibia, humerus, spine and pelvis
 - *Sarcomatous degeneration:* Deadly complication
 - It follows as rapid and fatal course.
 - It occurs in 5–10% of patients.

- Osteosarcoma occurs in 1% of patients.
- Men are affected commonly.
- Age: 70–80 years.
- Site: Femur, humerus and healed fractures.

- *Degenerative joint disease*
- *Cardiovascular abnormalities*
 - Increased cardiac output
 - Left ventricular hypertrophy
 - Congestive heart failure

Cherubism

(Synonyms: Familial fibrous dysplasia of jaws; disseminated juvenile fibrous dysplasia)

- Cherubism is an autosomal dominant fibro-osseous lesion of the jaws involving more than one quadrant that stabilizes after the growth period, usually leaving some facial deformity and malocclusion.
- It is a benign hereditary condition which affects only the jaw bones and is characterized by *bilaterally symmetrical enlargement* of mandible and sometimes maxilla.
- The term *cherubism* was first used by Jones to describe the clinical appearance of affected patients. They resemble *cherubs* who are the chubby cheeked little angels in renaissance paintings.

Pathogenesis

- Autosomal dominant inheritance.
- Cherubism occurs due to mutations in genes responsible for jaw development. The defect has variable expression and penetrance is mapped to chromosome 4p16.3 in fibroblast growth factor receptor-3 (FGFR-3).
- The excess bone formation is due to reduction in osteoclast formation and is caused by deficiency of sex steroids. At puberty, the increase in plasma concentration of oestradiol and testosterone causes localized increase of osteoclasts in children in cherubism and stabilizes the disease.

Clinical features

- Males are more commonly affected with greater severity.
- 100% penetrance is seen in males and 50–70% in females.

- It develops as early as 1 year of age (1–3 years). Rapidly progresses and slows down when patient reaches 5 years of age and stops by the age of 12–15 years.
- Bilateral, symmetrical swelling of mandibular body or maxillary tuberosities.
- Firm painless jaw expansion and deformity.
- Widened alveolar processes.
- Inverted V-shaped palatal arches.
- Premature exfoliation of primary teeth.
- Delayed permanent tooth eruption.
- Teeth displacement or resorption.
- Cervical lymphadenopathy.
- Condyles spared in most of the cases.
- Hypertelorism.
- A rim of sclera may be visible beneath the iris giving classic *eyes-to-heaven* appearance.
- It may be connected with other conditions like *Noonan's syndrome* —lesions in humerus, gingival fibromatosis, psychomotor retardation, orbital involvement and obstruction sleep apnoea.
- *Grading system by Arnott (1978)*
 - Grade I: Involvement of both mandibular ascending rami
 - Grade II: Involvement of both maxillary tuberosity and mandibular ascending rami
 - Grade III: McCune–Albright syndrome involvement of maxilla and mandible except the coronoid process and condyles.

Radiographic features

- Bilateral multilocular cystic expansion of jaws.
- Displacement of inferior alveolar canal.
- Presence of numerous unerupted teeth producing a radiographic appearance of *floating tooth syndrome.*
- In adulthood, the cystic areas become reossified with irregular patchy sclerosis.
- *Grading system by Kalantar Motamedi*
 - Grade I: Lesions of mandible without signs of root resorption.
 - Grade II: Mandibular and maxillary lesions without root resorption.
 - Grade III: Aggressive lesions of mandible with root resorption.
 - Grade IV: Both the jaws are involved and root resorption is present.

- Grade V: Rare, massively growing, aggressive and deforming juvenile cases involving the maxilla and mandible which may include the coronoid process and condyles.

Histopathology

- Multiple multinucleated giant cells together with ovoid to spindle-shaped cells within a fine fibrillar collagenous stroma.
- The multinucleated giant cells show strong positivity for tartrate resistant acid phosphatase suggesting that they are osteoclasts.
- Numerous small vessels with large endothelial cells and perivascular capillary cuffing.
- Eosinophilic cuffing is characteristic of cherubism.
- Healing lesions show increase in fibrous tissue and a decrease in number of giant cells, formation of new bone.

Prognosis and predictive factors

- No treatment is suggested.
- Patients seek medical attention for aesthetic and functional concerns.
- Orthodontic treatment for malocclusion.
- Surgical curettage, contouring or osteotomy for correcting gross facial deformities after puberty.
- Radiation therapy is discouraged due to increased risk of osteoradionecrosis and osteosarcoma.

Craniosynostosis syndromes

Craniosynostosis is a condition in which one or more of the fibrous sutures in an infant skull prematurely fuse by ossification, thereby changing the growth pattern of the skull. Because the skull cannot expand perpendicular to the fused suture, it compensates by growing more in the direction parallel to the closed sutures. Sometimes, the resulting growth pattern provides the necessary space for the growing brain, but results in an abnormal head shape and abnormal facial features. In cases in which the compensation does not effectively provide enough space for the growing brain, craniosynostosis results in increased intracranial pressure leading possibly to visual impairment, sleeping impairment, eating difficulties or an impairment of mental development combined with a significant reduction in IQ.

Craniosynostosis occurs one in 2000 births. Craniosynostosis is part of a

syndrome in 15–40% of the patients, but it usually occurs as an isolated condition. The most common craniosynostosis syndromes are Crouzon, Pfeiffer and Apert syndromes.

Crouzon syndrome

(Synonym: Craniofacial dysostosis)
Premature craniosynostosis occurs in association with wide variety of other abnormalities.

Pathogenesis

- Dysplasias of skeleton are caused by malformations of mesenchyme and ectoderm.
- Dysplasias are inherited in an autosomal dominant pattern.
- Mutation in fibroblast growth factor receptor-2 (FGFR-2) gene in 10q26 is responsible for Crouzon syndrome without acanthosis nigricans.
- *FGFR-3* gene mutation is seen in Crouzon syndrome with acanthosis nigricans.

Clinical features

- Early synostosis of cranial sutures, especially coronal and sagittal sutures.
- Fontanelles are not obliterated.
- Lateral and anteroposterior flattening of cranium.
- Forehead is high and wide.
- Hypoplastic maxilla.
- Deviation of nasal septum, narrowed/obliterated nares.
- Hypertelorism, divergent squint.
- Optic nerve atrophy leads to vision impairment because of intracranial hypertension.
- Loss of hearing.
- Malocclusion, malposed teeth and dysphagia.
- Syndromic acanthosis nigricans in axillary fossa.
- Headache, convulsions and mental retardation.

Radiographic features

Skull radiograph shows obliterated sulcus, shallow eye sockets, shortened anterior cranial fossa, underdeveloped lateral sinuses and bifid spine.

Apert syndrome

(Synonym: Acrocephalosyndactyly)

It is a rare autosomal dominant disorder characterized by craniosynostosis, craniofacial anomalies and severe symmetric syndactyly (cutaneous and bony fusion) of hands and feet.

Pathogenesis

- It is caused by specific missense substitution mutations, i.e. Ser252Trp, Ser252Phe, Pro253Arg involving fibroblast growth factor receptor-2 (FGFR-2), which maps to chromosome 10q25–26.
- FGFR-2 mutation causes increased number of precursor cells that enter the osteogenic pathway, which forms subperiosteal bone matrix formation and premature calvaria ossification during fetal development.
- Syndactyly of Apert syndrome is caused by keratinocytes growth factor receptor (KGFR) mediated effect.

Clinical features

- Sex: No gender predilection.
- Craniosynostosis: Coronal sutures resulting in acrocephaly, brachycephaly, flat occiput and high prominent forehead.
- Syndactyly of hands and feet.
- Slanting palpebral fissures, hypertelorism, shallow orbits, proptosis and exophthalmos.
- Mitten hands and sock feet.
- Maxillary hypoplasia.
- High-arched palate, cleft palate, bifid uvula.
- Malocclusion.
- Delayed eruption, ectopic eruption.
- Shovel-shaped incisors.

Mandibulofacial dysostosis

(Synonym: Treacher Collins syndrome)

- Treacher Collins syndrome (TCS) is an inherited disorder characterized by diminished growth of craniofacial structures derived from the first and second pharyngeal arches.
- This syndrome was named after the eminent British ophthalmologist

Edward Treacher Collins.

Pathogenesis

- Inheritance of TCS is autosomal dominant, caused by mutations in the *TCOF1* gene, with complete penetrance and variable expressivity.
- Failure of neural crest cells to migrate into the first and second branchial arches leads to dysplasia, hypoplasia, or aplasia of the musculoskeletal derivatives of these arches. Therefore, the abnormalities are bilateral and symmetrical.
- The critical period occurs approximately between the 6th and 7th week of embryonic development.

Clinical features

- Sex: No sex predilection.
- Abnormalities are usually present bilaterally and symmetrically.
- The palpebral fissures are short and slope laterally downward.
- In the outer third of the lower lid, a coloboma is present, and the eyelashes may be deficient.
- The nose is of normal size; however, it appears large because of hypoplastic supraorbital rims and hypoplastic zygomas.
- The palpebral fissures are downward sloping, the cheek bones are depressed, the pinnae are malformed with widely varying severity, and the chin recedes with a large, down-turned mouth.
- Hypoplasia of malar bones, zygomatic process and mandible.
- Malformation of external ear.
- Macrostomia.
- Blind fistulae between angles of mouth and ears.
- Atypical hair growth.
- A cleft palate is found in one-third of patients with Treacher Collins syndrome.
- The parotid glands are missing or hypoplastic.
- Pharyngeal hypoplasia is a constant finding.

Radiographic features

- The mandibular angle is more obtuse than normal and the ramus is deficient.
- The coronoid and condylar processes are flat or aplastic.

Prognosis and predictive factors

- Distraction osteogenesis to lengthen the neonatal mandible.
- Corrective surgeries for skeletal deformities are usually deferred until skeletal maturity.

Pierre robin syndrome

(Synonyms: Pierre Robin sequence; Pierre Robin anomalad)

- The syndrome is named after the French dental surgeon Pierre Robin (1867–1950).
- Pierre Robin syndrome (PRS) is characterized by severe underdevelopment of lower jaw (retrognathia), downward or backward positioned tongue (glossoptosis), respiratory obstruction and cleft palate.
- PRS is called as *sequence* because the underdeveloped lower jaw begins a sequence of events, which lead to abnormal displacement of tongue and subsequent formation of cleft palate.

Pathogenesis

- The exact cause is unknown.
- Three pathophysiological theories are as follows:
 1. *The neurological maturation theory:* A delay in neurological maturation is noted in electromyography of the tongue musculature, the pharyngeal pillars and the palate, which may be due to the spontaneous correction of majority of cases with age supporting this theory.
 2. *The rhombencephalic dysneurulation theory:* In this theory, the motor and regulatory organization of rhombencephalus is related to a major problem of ontogenesis.
 3. *The mechanical theory:* Normally, between 9 and 11 weeks of gestation, the tongue moves down and away from the roof of mouth, allowing space for the lateral palatal shelves to shift to midline and fuse. However, in PRS, the small lower jaw keeps the tongue positioned higher in mouth than normal, thereby interfering with the normal closure of the palate. This typically results in a wide U-shaped cleft of soft and hard palate.

Clinical features

- Sex: No sex predilection.
- Mandibular micrognathia: Small body, obtuse gonial angle, posteriorly located condyle.
- Hypoplasia of mandible produces a typical *bird face.*
- Glossoptosis.
- Respiratory and feeding problems in the infant.
- Obstructive sleep apnoea.
- Cleft palate.
- Respiratory difficulty because tongue falls backward due to micrognathia and partially obstructs the epiglottis.
- Congenital heart defects, skeletal abnormalities and ocular lesions are also observed.

Prognosis and predictive factors

- Infants with this condition should not be put on their back, to prevent the tongue from falling back into the airway.
- Tracheostomy for airway blockade.
- Corrective surgery for cleft palate is indicated in between 9–12 months of age.

Achondroplasia

(Synonyms: Chondrodystrophia fetalis; fetal rickets)

- Achondroplasia is a disorder of the skeletal system that belongs to a group of diseases known as chondrodystrophies. This disorder involves a disturbance in the development of cartilage of the long bones (e.g. arms and legs). They frequently cause a disproportionately short stature (dwarfism).
- It is a non-lethal form of chondrodysplasia.
- In achondroplasia, there is an abnormality in the conversion of cartilage into bone at the growing ends (epiphyses) of the long bones. This process prevents the bones from further growth which ceases at a relatively early age.
- It is a disorder of bone growth that causes the most common type of dwarfism.

Pathogenesis

- It is transmitted as an autosomal dominant trait with complete

penetrance.
- Mutations in the fibroblast growth factor receptor 3 gene which has been mapped to chromosome 4p16.3.
- Mutations cause gain in gene function resulting in decreased endochondral ossification, inhibited proliferation of chondrocytes in growth plate cartilage and decreased cartilage production.

Clinical features

- Short stature, rhizomelic shortening of arms and legs, long trunk and trident hands.
- Abnormal hand appearance with persistent space between the long and ring fingers.
- Mid-facial hypoplasia, frontal bossing and limitation of joint motion.
- Disproportionate size of head in relation to remainder of the body.
- Achondroplastic dwarfs are of normal intelligence.
- Unusual strength and agility is present, so some are led to adopt occupation of professional wrestler.
- *Oral manifestations*
 - Retruded maxilla and relative mandibular prognathism
 - Malocclusion
 - Congenitally missing teeth

Radiographic features

- Lateral skull radiograph: Mid-face hypoplasia, enlarged calvaria, frontal prominence and shortening of base of skull.
- Diminished size of foramen magnum.
- Long bones show thickening and mild clubbing at ends.
- Epiphysis may close either early or late.
- Bones of skull fuse prematurely.

Histopathology

- Failure of endochondral ossification.
- Intramembranous and periosteal ossification is undisturbed.
- Disarray of chondrocytes, loss of columnation and normal chondrocyte proliferation.
- Because endochondral growth is affected, the orderly growth is disrupted resulting in stunting of bone.

- Intramembranous ossification is normal leading to normal clavicles and skull.

Prognosis and predictive factors

- There is no specific treatment for achondroplasia.
- Related abnormalities, including spinal stenosis and spinal cord compression, should be treated, when they are symptomatic.

Chondroectodermal dysplasia

(Synonym: Ellis–van Creveld syndrome)
Chondroectodermal dysplasia is an inherited skeletal disorder characterized by chondrodysplasia, ectodermal dysplasia and polydactyly with congenital heart defects.

Pathogenesis

Autosomal recessive mode of inheritance caused by a mutation in the *EVC1* and *EVC2* genes on chromosome 4p16.

Clinical features

- No sex predilection.
- Disproportionate dwarfism, postaxial polydactyly, ectodermal dysplasia, a small chest and a high frequency of congenital heart defects.
- Cleft lip or palate.
- Undescended testicle *(cryptorchidism).*
- Nail problems, including missing or deformed nails.
- Short arms and legs, especially forearm and lower leg.
- Short height.
- Sparse, absent, or fine textured hair.
- *Oral manifestations*
 - A fusion of the anterior portion of the upper lip to the maxillary gingival margin, resulting in an absence of mucobuccal fold and the upper lip to present a slight V-notch in the middle.
 - Short upper lip, bound by frenula to alveolar ridge (lip tie).
 - Often serrated lower alveolar ridge.
 - Teeth may prematurely erupt at birth or exfoliate prematurely.
 - Neonatal teeth, partial anodontia, small teeth, and delayed eruption.

- Enamel hypoplasia may result in abnormally shaped teeth with frequent malocclusion.

Prognosis and predictive factors

- Many babies with this condition die in early infancy, usually due to a small chest or heart defect.
- Stillbirth is common.

Cleidocranial dysplasia

(Synonyms: Marie and Sainton's disease; cleidocranial dysostosis)

Cleidocranial dysplasia (*cleido*—collar bone, *cranial*—head, *dysplasia*—abnormal formation) is a hereditary condition characterized by defective development of the cranial bones and by the complete or partial absence of the clavicles.

Pathogenesis

- It is transmitted as an autosomal dominant trait with complete penetrance and variable expressivity.
- Mutation in *core binding factor alpha-1 (CBFA-1)* gene located on chromosome 6p21.
- Recent study suggests that the CBFA1 gene additionally plays an important role in odontogenesis via participation in odontoblast differentiation, enamel organ formation and dental lamina proliferation—so, dental anomalies are seen.

Clinical features

- It is characterized by abnormalities of skull, teeth, jaws, shoulder girdle and long bones.
- In skull, the fontanelles often remain open or show delayed closing.
- The sutures may remain open and wormian bones are common.
- Sagittal suture is sunken and gives flat appearance of skull.
- Frontal, parietal and occipital bones are prominent.
- Paranasal sinuses are underdeveloped.
- Brachycephalic skull.
- Calvarial thickening of supraorbital part of frontal bone, squamous part of temporal and occipital bones.

- Complete to partial absence or thinning of one or both clavicles is seen. Because of these clavicular disturbances, the patients may have unusual mobility of shoulders and may be able to bring their shoulders forward.
- Defects in vertebral column, pelvis, long bones and digits.
- *Oral manifestations*
 - High or narrow arched palate and cleft palate.
 - Underdeveloped maxilla and larger mandible.
 - Prolonged retention of deciduous teeth and delayed eruption of permanent teeth.
 - Roots of teeth are shorter and thinner and may be deformed.
 - Absence or paucity of cellular cementum on the roots of permanent teeth and this may be related to failure to eruption.
 - Numerous unerupted supernumerary teeth.

Radiographic features

- Patent anterior fontanelle, wormian bones are commonly seen in skull.
- Partial or complete absence of clavicle is seen.
- Broadening of metacarpal, carpal and metatarsal bones are seen.

Prognosis and predictive factors

- Dental problems are the most significant complications.
- Orthodontic treatment for malocclusion.
- Applying dentures over the unerupted teeth.
- It is suggested that the removal of primary or supernumerary teeth does not promote eruption of unerupted permanent teeth. In addition, permanent teeth may be difficult to extract due to malformed roots.

Down syndrome/trisomy 21 syndrome

(Synonyms: Trisomy 21 syndrome; mongolism; congenital acromicria syndrome)

- Down syndrome is named after Dr Langdon Down (1866), who first described the syndrome as a disorder.
- Down syndrome is a form of mental retardation associated with characterized morphological features and many somatic abnormalities due to chromosomal aberrations.

Pathogenesis

- Genes on an extra copy of chromosome 21 are responsible for all characteristics associated with Down syndrome. Normally, each human cell contains 23 pairs of different chromosomes. However, sometimes a person inherits an extra chromosome from one of the parents resulting in *trisomy 21*. About 95% of individuals with Down syndrome inherit an entire extra chromosome 21.
- Approximately 3–4% of individuals with Down syndrome do not inherit an entire extra chromosome 21, but just some extra chromosome 21 genes, which are attached to another chromosome (usually chromosome 14). This is called a *translocation*. Most of the time, translocations are random events during conception.
- About 2–4% of people with Down syndrome inherit additional genes from chromosome 21, but not in every cell of the body. This is known as *mosaic Down syndrome*. It is so mild that it may go undetected.

Clinical features

- It is the leading cause of cognitive impairment.
- Down syndrome is associated with mild to moderate learning disabilities, developmental delays, characteristic facial features, and low muscle tone in early infancy.
- Many individuals with Down syndrome also have heart defects, leukaemia, early onset Alzheimer's disease, gastrointestinal problems, and risk of dislocation.
- The level of mental retardation varies from patient to patient, but is usually moderate. Adults with Down syndrome have an increased risk for dementia.
- Small and misshapen ears with abnormalities of folds are observed.
- Upward slanting eyes and the inner corner of the eyes may be rounded instead of being pointed.
- White spots on the coloured part of the eye *(Brushfield spots).*
- Wide, short hands with short fingers, single crease in the palm of the hand.
- Physical development is often slower than normal.
- Sleep apnoea (because the mouth, throat, and airway are narrowed in children with Down syndrome).
- Hypothyroidism.
- *Oral manifestations*:
 - Small mouth with protrusion of tongue (macroglossia) with difficulty in

eating and speaking, scrotal tongue, hypoplasia of maxilla, delayed tooth eruption, partial anodontia, enamel hypoplasia, juvenile periodontitis and cleft lip or palate are noticed.

- Delayed tooth eruption and ectopic eruption are common.
- Fissuring and thickening of lips, and angular cheilitis are frequently seen.
- Cheilitis occurs frequently in children due to mechanical factors, trauma, actinic influence, atopy, avitaminosis or low-grade infections like candidiasis.
- Fissured tongue and juvenile periodontitis are seen.

Prognosis and predictive factors

- There is no specific treatment for Down syndrome. Severe heart problems and leukaemia may lead to early death.
- A child born with a gastrointestinal blockage may need major surgery immediately after birth. Certain heart defects may also require surgery.
- Orthodontic treatment for malocclusion.

Fibro-osseous lesions of jaws

- Fibro-osseous lesions are a diverse group of disorders of bone characterized by replace-ment of normal bone with a fibrous connective tissue matrix containing abnormal bone or cementum.
- The designation *fibro-osseous lesion* is not a specific diagnosis and it describes only a process.

Classification

Classification of fibro-osseous lesions of jaws is given in Table 16.1.

- They are heterogenous group of lesions with a diverse cause, behaviour and prognosis but similar histological features and overlapping clinical and radiographic features.
- Although they have been grouped under the encompassing heading of *benign fibro-osseous lesions*, a more specific diagnosis often is critical because the treatment of these diseases varies from none to surgical recontouring to complete removal.
- So, an accurate diagnosis is extremely important and is possible only by careful correlation of clinical, radiographic and histological features.

Table 16.1

Classification of fibro-osseous lesions of jaws

According to Waldron
1. Fibrous dysplasia 2. Reactive (dysplastic) lesions arising in the tooth bearing area: a. Periapical cemento-osseous dysplasia b. Focal cemento-osseous dysplasia c. Florid cemento-osseous dysplasia 3. Fibro-osseous neoplasms: a. Cementifying fibroma b. Ossifying fibroma c. Cemento-ossifying fibroma
According to Pieter J Slootweg and Hellmuth Muller
1. Group I: Fibrous dysplasia 2. Group II: Juvenile ossifying fibroma 3. Group III: Ossifying fibroma 4. Group IV: Cemento-osseous dysplasia

Fibrous dysplasia

The term *fibrous dysplasia* (FD) was coined by *Lichtenstein in 1938.*

Definition (WHO, 2005)

It is a benign, self-limiting but non-encapsulated lesion, which occurs mainly in young subjects, usually in the maxilla, and shows replacement of the normal bone by a cellular fibrous tissue containing islands or trabeculae of metaplastic bone.

Pathogenesis

- The exact aetiology is unknown.
- Mutations in *GNAS1* (guanine nucleotide–binding protein, alpha stimulating activity polypeptide) gene on 20q13.2.
- This gene encodes G-protein that stimulates the production of cyclic-AMP.
- The mutation of the gene causes continuous activation of G-proteins that stimulates production of cyclic AMP leading to hyperfunction and proliferation of affected cells.
- When endocrine cells are affected, they result in precocious puberty, hyperthyroidism, overproduction of growth hormone and cortisol.

- When melanocytes are affected, their increased proliferation causes *café-au-lait* spots.
- When osteoblasts are affected, they lead to monostotic or polyostotic fibrous dysplasia.

Clinical features

The following four clinical forms are identified:
1. Monostotic FD
2. Polyostotic FD
3. Craniofacial FD
4. Cherubism

Monostotic fibrous dysplasia

- 70–80% of fibrous dysplasias are of monostotic form.
- The degree of bone deformity is less severe compared to polyostotic form.
- Location: Ribs, femur, tibia, craniofacial bones and humerus.
- This form presents with pain or pathologic fracture in patients aged 10–70 years.
- *Leontiasis ossea* is the name given to fibrous dysplasia that affects maxilla and gives the patient a leonine appearance.

Polyostotic fibrous dysplasia

- 20–30% of fibrous dysplasias are of polyostotic form.
- Location: Skull and facial bones, spine and shoulder girdle, femur, tibia, pelvis, ribs, upper extremities, and clavicle.
- The dysplasia may be unilateral or bilateral.
- It affects several bones of a single limb or both limbs with or without axial skeletal involvement.
- Involvement is asymmetric and generalized, when disease is bilateral.
- The initial symptom is pain in the involved limb associated with a lump, spontaneous fracture or both.
- The structural integrity of bone is weakened and weight-bearing bones become bowed. The curvature of femoral neck and proximal shaft of femur markedly increase causing a *shepherd's crook deformity,* a characteristic sign.
- Two types:
 1. Fibrous dysplasia involving a variable number of bones, accompanied by pigmented lesions of skin or café-au-lait spots—

Jaffe's type.

2. Severe fibrous dysplasia involving nearly all bones in skeleton and accompanied by pigmented lesions of skin and endocrine disturbances—*Albright's syndrome.*

Craniofacial fibrous dysplasia

- This pattern of disease occurs in 10–25% of patients with monostotic form and 50% with the polyostotic form.
- It also occurs in an isolated craniofacial form (no extracranial lesions are present).
- Location: Frontal, sphenoid, maxillary and ethmoidal bones.
- Hypertelorism, cranial asymmetry, facial deformity, visual impairment, exophthalmos and blindness may occur because of involvement of orbital and periorbital bones.
- Involvement of sphenoid wing and temporal bones causes vestibular dysfunction, tinnitus and hearing loss.
- Cribriform plate involvement causes hyposmia or anosmia.

Cherubism

- It is an autosomal dominant disorder of variable penetrance.
- It occurs in children and usually among males.
- Regression may occur after adolescence.
- Jaw is broad and protruding.

Already explained on page 424 of this chapter.

Oral manifestations

- Commonly mandible is involved.
- Expansion and deformity of jaws and the eruption pattern of teeth are disturbed because of the loss of normal support of developing teeth.
- The endocrine disturbances may also alter the teeth eruption.
- No intraoral pigmentation is reported.

Radiographic features

Radiographic features are extremely variable:

- Unilocular radiolucency.
- Multilocular radiolucency with a relatively well-circumscribed border and containing a network of fine bony trabeculae which gives typical mottled

appearance.

- Many delicate trabeculae in different directions get superimposed giving rise to *ground-glass* or *peau d'orange* appearance.
- The lesion merges with adjacent normal bone.

Histopathology (fig. 16.2)

- Fibrous connective tissue made up of proliferating fibroblasts is a compact stroma of interlacing collagen fibres.
- *Chinese letter* or *C-shaped* irregular trabeculae of bone are scattered throughout lesion.
- Osteoblastic rimming on the surfaces of trabeculae are absent.
- Osteoclastic activity may be seen in few areas.

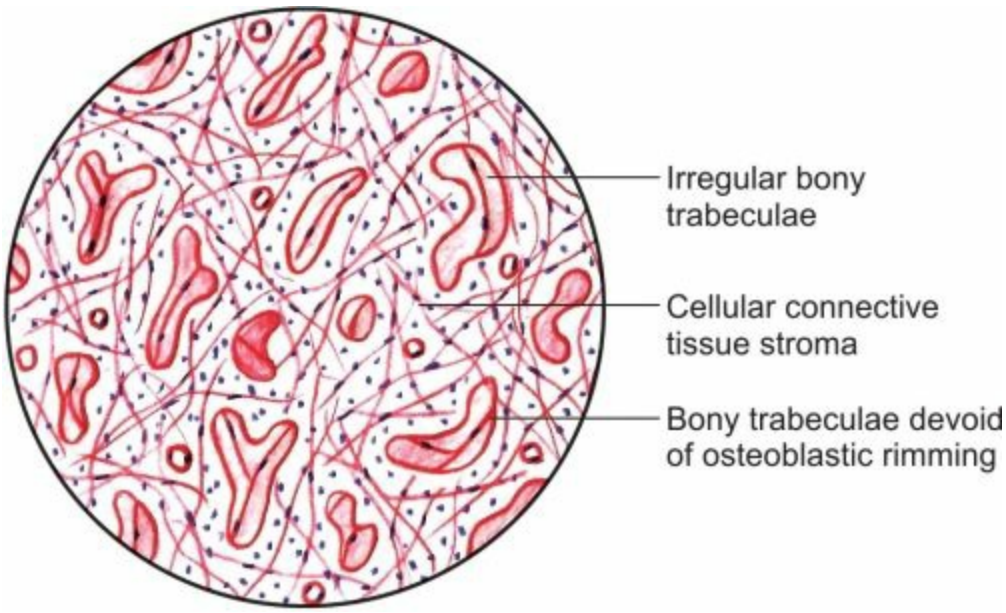


FIG. 16.2 Fibrous dysplasia.

Prognosis and predictive factors

- Smaller lesions may be surgically resected.
- The large lesions preclude removal without extensive surgery.
- In many cases, the disease tends to stabilize and essentially stops enlarging when skeletal maturation is reached.
- Some patients with minimal cosmetic or functional deformity may not require or desire surgical treatment.

Focal cemento-osseous dysplasia

(Synonyms: Periapical osteofibroma; periapical fibrous dysplasia; periapical fibro-osteoma; periapical fibro-osteocementoma; sclerosing cementoma, cementoblastoma)

Definition

- It is a non-neoplastic lesion affecting the periapical tissues of one or more teeth and with histologic features similar to those of the lesions of the cemento-ossifying fibroma group, but without a sharply defined margin.
- Focal cemento-osseous dysplasia (FocCOD) was first described by Brophy (1915).

Pathogenesis

- The exact aetiology is unknown. However, chronic inflammation or slight trauma may have an important role for formation.
- The *first stage* is characterized by proliferation of a cellular fibrous connective tissue. During the *second stage*, bone and/or cementum is formed within the fibrous tissue, giving the lesion a characteristic radiolucent/radiopaque appearance. The *final stage* of maturation is characterized by continuous progressive formation of bone and/or cementum. A narrow rim of connective tissue usually surrounds the hard tissue masses.

Clinical features

- **Age.** 14–82 years.
- **Gender.** Female predilection.
- **Location.** It is commonly seen in premolar–molar area of mandible.
- **Signs and symptoms**
 - Usually, it is asymptomatic and most often found accidentally on routine radiographs. Sometimes, patients have symptoms such as local jaw expansion and mild discomfort.
 - Vitality tests of affected teeth are usually positive.

Radiographic features

FocCODs present with three different appearances, according to their developmental stage:

1. *The initial osteolytic stage* is characterized by radiolucency of the periapical

areas of involved teeth, often in the anterior mandible. It is easily been mistaken for periapical pathology.
2. *The second intermediate stage* is characterized by radiopaque foci in an otherwise rarefied translucent area.
3. *The final mature stage* reveals a characteristic radiographic appearance: Well-defined radiopacities surrounded by a radiolucent halo.

Histopathology

- It characteristically occurs in the tooth-bearing areas of the jaws, and lesions are closely associated with the apices of teeth.
- FocCODs have three developmental stages, so the ratio of fibrous tissue to mineralized material may vary; it has been demonstrated that FocCODs are initially fibroblastic but, over the course of several years, they show increasing degrees of calcification.

Note: Slootweg considered a sharply defined margin as the only distinguishing feature between cemento osseous fibroma and FocCODs.

- FocCODs are characterized by thick, curved or linear bone trabeculae *(ginger root pattern)* or irregularly shaped cementum-like masses.
- Hard tissues consist of spherical and trabeculae shaped cementum-like structures with irregular, basophilic reversal lines. Smaller cementicle-like structures and trabecular woven bone may be observed at the periphery of the lesion.

Prognosis and predictive factors

- Surgical excision.
- Recurrence is rare.

Florid cemento-osseous dysplasia

Definition

Florid cemento-osseous dysplasia (FCOD) is a lobulated mass of dense, highly mineralized, almost acellular cemento-osseous tissue typically occurring in several parts of the jaws, sometimes it shows familial

distribution.

Pathogenesis

FCOD appears to be inherited as an autosomal dominant trait with variable phenotypic expression.

Clinical features

- **Age.** 19–76 years.
- **Gender.** Female predilection.
- **Location.** Posterior region of mandible.
- **Signs and symptoms**
 - The *classic FCOD* is characterized by symmetric bony hard swellings of the jaws, often involving all four quadrants.
 - Lesions are reported to be florid, involving large areas of the jaws.
 - The masses may become large and cause considerable facial deformity.
 - There may be spacing between teeth with some degree of displacement.
 - Teeth associated with areas are non-infected. They are usually vital.
 - Symptoms such as pain or drainage are mostly associated with exposure of the sclerotic calcified masses in the oral cavity.
 - Clinically, purulent discharge or fistula formation may occur as secondary phenomena and cemento-osteomyelitis with sequestration may occasionally develop.

Radiographic features

- The radiographic appearance of FCOD depends on the degree of maturation of the lesions.
- Immature FCOD lesions appear in radiolucent area, whereas later stages of maturation are characterized by dense radiopaque masses of cemento-osseous material.
- In panoramic radiographs, FCODs appear as diffuse, lobular, irregularly shaped radiopacities.
- In some cases, lesions are enmeshed within poorly defined areas of decreased radiodensity and have a *ground glass* appearance.
- If the lesion is infected, a radiolucent border is often discernible.

Histopathology

- Early stage lesions are characterized by rounded globules or irregular

cementum trabeculae of varying size in a cellular fibroblastic stroma.
- Some cases may show a proliferative component at the periphery of the lesion. This component consists of cellular fibrous tissue containing rounded globules and/or cementum trabeculae.
- Sometimes signs of infection, resorption, necrosis and sequestration are seen.
- Most cases exhibit a mixture of cementum-like material and irregular trabeculae of bone, with some trabeculae rimmed by plump osteoblasts and others showing active resorption with apposed multinucleated osteoclasts.

Prognosis and predictive factors

- Surgical excision.
- Recurrence is rare.

Periapical cemento-osseous dysplasia

(Synonyms: Osseous dysplasia; cemental dysplasia; cementoma)
It predominantly involves the periapical region of anterior mandible. The solitary lesions may occur, but multiple foci are present more frequently.

Clinical features

- **Age.** 30–50 years.
- **Gender.** Female predilection.
- **Location.** Posterior region of mandible.
- **Signs and symptoms**
 - Teeth associated with lesion are usually vital and seldom have restorations.
 - Asymptomatic condition, that is discovered when radiographs are taken for other purposes.
 - Each lesion is self-limiting and does not typically expand the cortex.

Radiographic features

- Early lesions appear as circumscribed areas of radiolucency involving the apical area of a tooth (at this stage, the lesion cannot be differentiated radiographically from a periapical granuloma or periapical cyst).
- The lesions tend to mature over time to create a mixed radiolucent and

radiopaque appearance.
- In end stage, the lesions show a circumscribed dense calcification surrounded by a narrow radiolucent rim.

Histopathology

Similar to FCOD or FocCOD.

Prognosis and predictive factors

- Surgical excision.
- Recurrence is rare.

Diseases of temporomandibular joint (TMJ)

Developmental disturbances of TMJ

Aplasia of mandibular condyle

Aplasia of mandibular condyle may occur unilaterally or bilaterally, but in either event is a rare condition.

Clinical features

- It is frequently associated with other anatomically related defects such as a defective or absent external ear, an underdeveloped mandibular ramus or microstomia.
- If the condylar aplasia is unilateral, there is obvious facial asymmetry, both occlusion and mastication may be altered. A shift of the mandible toward the affected side occurs during opening.
- In bilateral cases, this shift is not present.

Prognosis and predictive factors

Treatment of condylar aplasia consists of osteoplasty, if the derangement is severe, correction of the malocclusion by orthodontic appliances.

Hypoplasia of mandibular condyle

- Underdevelopment or defective formation of the mandibular condyle may be congenital or acquired.
- *Congenital hypoplasia:* Idiopathic in origin and it may be unilateral or bilateral.
- *Acquired form of hypoplasia:* It may be due to any agent which interferes with the normal development of the condyle. It may occur in forceps deliveries that cause traumatic birth injury. External trauma to the condylar area in infants or younger children may also result in hypoplasia. In some cases, children following X-ray radiation over the TMJ area for local treatment of skin lesion such as haemangioma or birth mark.
- Infection spreading locally from the dental area or by the haematogenous route from a distant site may involve the joint, interfere with condylar growth and result in a hypoplastic condyle.

Clinical features

- The clinical deformity depends upon whether the disturbance has affected one or both condyles and upon the degree of the malformation. This, in turn, is directly related to the age of the patient at the time of involvement, duration of the injury and its severity.
- Unilateral involvement is a common clinical type.
- Severe unilateral arrest of growth will produce facial asymmetry, often accompanied by limitation of lateral excursion on one side and exaggeration of the antegonial notch of the mandible on the involved side.
- A mild disturbance causes lesser degree of facial asymmetry, accompanied by mandibular midline shift during opening and closing.
- The distortion of the mandible results from lack of downward and forward growth of the body of the mandible due to the arrest of the chief growth centre of the mandible and the condyle.
- The older the patient at the time of growth disturbance, the less severe will be the facial deformation (growth of the condyle persists until the age of 20 years).

Prognosis and predictive factors

- Treatment of condylar hypoplasia is a difficult problem since there are no available means of stimulating its growth locally or compensating for its failure.
- Cartilage or bone transplantation and/or unilateral or bilateral sliding osteotomy can be done to improve the appearance of the patient with asymmetry and retrusion.

Hyperplasia of mandibular condyle

It is a rare unilateral enlargement of the condyle which resembles neoplasm of this structure.

Pathogenesis

The exact cause of this condition is unknown, but it has been suggested that mild chronic inflammation, resulting in a condition analogous to a proliferative osteomyelitis, stimulates the growth of the condyle or adjacent tissues. The unilateral occurrence strongly suggests that it is a local phenomenon.

Clinical features

- It usually exhibits a unilateral, slow progressive elongation of the face with deviation of the chin away from the affected side.
- The enlarged condyle may be clinically evident or at least palpated and presents a striking radiographic appearance in both anteroposterior and lateral views as well as in specific condylar films.
- The affected joint may or may not be painful.
- A severe malocclusion is usually sequelae of the condition.

Prognosis and predictive factors

- The treatment of condylar hyperplasia usually involves resection of the condyle.
- This is generally sufficient to restore normal occlusion, although complete correction of the facial asymmetry may not be accomplished by this procedure.

Traumatic disturbances of TMJ

Luxation and subluxation

- Dislocation of the TMJ occurs when the head of the condyle moves anteriorly over the articular eminence into such a position that it cannot be returned voluntarily to its normal position.
- Some authors believe that this inability to retrude the mandible is caused by spasm of the temporal muscle initiated by myotactic reflex. Thus, in movements of the mandible involving forward translation of the condyle, tension may be placed on the temporalis leading to formation of the muscle spasm.
- *Luxation* of the joint refers to complete dislocation, while *subluxation* is a partial or incomplete dislocation, actually a form of hypermobility.

Pathogenesis

- Traumatic injury.
- Stretching of capsule, usually at the point of attachment for the external pterygoid muscle into the capsule.
- Yawning.
- Wide mouth opening during tooth extraction or while removing tonsils or

while using mouth prop.

Clinical features

- It is characterized by sudden locking and immobilization of the jaws.
- Prolonged spasmodic contraction of the temporal, internal pterygoid and masseter muscles, with protrusion of the jaw.
- All activities requiring motion of the mandible, such as eating or talking are impossible.
- Superior and posterior dislocation of the condyle may occur rarely as the result of an acute traumatic impaction injury and the head of the condyle may be forced through the glenoid fossa or tympanic plate into the middle cranial fossa.

Prognosis and predictive factors

- Reduction of a dislocated condyle is accomplished by inducing relaxation of the muscles and then guiding the head of the condyle under the articular eminence into its normal position by an inferior and posterior pressure of the thumbs in the mandibular molar area.
- The necessary relaxation can sometimes be brought about only by means of general anaesthesia or by tiring the masticatory muscles by cupping the chin in the palm of the hand and applying a posterior and superior pressure for 5–10 minutes.

Ankylosis of TMJ

Ankylosis of the TMJ is one of the most incapacitating diseases of TMJ.

Pathogenesis

Aetiology. Straith and Lewis enumerated the aetiologic factors as follows:

- Abnormal intrauterine development
- Birth injury (by forceps particularly)
- Trauma to the chin forcing the condyle against the glenoid fossa, particularly with bleeding into the joint space
- Malunion of condylar fractures
- Injuries associated with fractures of the malar–zygomatic compound
- Loss of tissues with scarring
- Congenital syphilis
- Primary inflammation of the joint (rheumatoid arthritis, infectious

arthritis, Marie–Strumpell disease)
- Inflammation of the joint secondary to a local inflammatory process (e.g. otitis media, mastoiditis, osteomyelitis of the temporal bone or condyle)
- Inflammation of the joint secondary to a bloodstream infection (e.g. septicaemia, scarlet fever)
- Metastatic malignancies
- Inflammation secondary to radiation therapy.

Clinical features

- **Age.** It occurs at any age, but most cases occur before the age of 10 years.
- **Gender.** No sex predilection.
- **Signs and symptoms**
 - The patient may or may not be able to open mouth to any appreciable extent depending on the type of ankylosis.
 - In complete ankylosis or bony ankylosis, there will be bony fusion with absolute limitation of motion.
 - In incomplete ankylosis or fibrous ankylosis, limited jaw movement is seen.
 - Facial deformity depends upon unilateral or bilateral ankylosis.
 - Unilateral ankylosis occurring at an early age, the chin is displaced late backward on the affected side because of a failure of development of the mandible. The chin deviates toward the ankylosis side while opening the motion.
 - Bilateral ankylosis occurring in childhood results in underdevelopment of the lower portion of the face, a receding chin and micrognathia.
 - TMJ ankylosis has been divided into two types, depending upon the anatomic site of the ankylosis with respect to joint itself:
 1. Intra-articular ankylosis
 2. Extra-articular ankylosis
 - In intra-articular ankylosis, the joint undergoes progressive destruction of the meniscus with flattening of the mandibular fossa, thickening of the head of the condyle and narrowing of the joint space. The ankylosis is basically fibrous, although ossification in the scar may result in a bony union. No movement is present.
 - In extra-articular ankylosis, splinting of the TMJ by a fibrous or bony mass external to the joint proper, as in cases of infection in surrounding bone or extensive tissue destruction. Movement is present.

Radiographic features

Abnormal or irregular shape of the head of the condyle and a radiopacity indicative of the dense bone filling the joint space.

Prognosis and predictive factors

- Treatment of TMJ bony ankylosis is surgical, usually complicated by the concomitant under development of the jaw.
- The operation consists of osteotomy or removal of a section of bone below the condyle.
- Fibrous ankylosis may be treated by functional methods.

Inflammatory disturbances of TMJ

Inflammation of joints is known as *arthritis.* There are three common types of inflammatory disturbances of joints:

1. Arthritis due to a specific infection
2. Rheumatoid arthritis
3. Osteoarthritis or degenerative joint disease—rarely affects TMJ, since it is not a weight-bearing joint.

Arthritis due to a specific infection

- Rarely occurs.
- There is a gamut of infections (such as those resulting from the gonococci, streptococci, staphylococci, pneumococci, and the tubercle bacillus) which may produce polyarticular involvement, either by bloodstream or by lymphatic metastasis or by direct extension from a focal infection. But, the TMJ uniquely appears to escape such infection in most cases except in the event of gonococcal infection.
- Commonly, it is caused by direct extension of infection into the joint as a result of an adjacent cellulitis or osteomyelitis. Other infections like dental infection, infection of the parotid gland, facial or ear infection may extend to cause arthritis.

Clinical features

- Severe pain in the joint with extreme tenderness on palpation or manipulation over the joint area.
- The motion is limited due to severe pain.
- Healing of this form of arthritis often results in ankylosis, either osseous

or fibrous.
- Fibrous ankylosis is more common, but in either event there is severe limitation of motion.

Histopathology

- Depending upon the severity of involvement, there is a variable amount of destruction of the articular cartilage and articular disc.
- The joint spaces become obliterated in the healing phase by the development of granulation tissue and its subsequent transformation into dense scar tissue.
- In time, the disc may become completely replaced and the entire joint space may be filled with the cicatrix.

Prognosis and predictive factors

- The treatment of an infectious arthritis is chiefly the administration of antibiotics.
- If treatment is instituted in the acute phase, the sequelae will be less deforming or disabling than if the disease has been allowed to enter a chronic phase.
- In the advanced cases, meniscectomy or condylectomy has been advocated.

Rheumatoid arthritis

Rheumatoid arthritis is a chronic autoimmune disorder characterized by non-suppurative inflammatory destruction of the joints.

Pathogenesis

- The exact aetiology is unknown.
- It may result from a cross-reaction of antibiotics generated against haemolytic streptococci or other microorganisms or may represent an antibody attack against bacterial cell wall or viral capsule fragments deposited within the synovium.
- Few cases show familial pattern. It begins as an attack against the synovial membrane (synovitis). A reactive macrophage-laden fibroblastic proliferation from the synovium creeps on to the joint surface. This releases collagenases and other proteases, which destroy the cartilage and underlying bone. Attempted remodelling by the damaged bone results in

a characteristic deformation of the joint.

Clinical features

- **Age.** 25–45 years.
- **Sex.** Female predilection.
- **Signs and symptoms**
 - Sites: Knees and elbows, hip joints, and small joints of hands and feet.
 - In early stages, slight fever, loss of weight and fatigue ability are seen.
 - Signs and symptoms become more severe over time and include swelling, pain, stiffness, joint deformity and disability with possible fibrous or bony fusion of opposing articular surfaces (ankylosis).
 - Periods of remission often interspersed with periods of exacerbation.
 - Firm partially movable, non-tender rheumatoid nodules beneath the skin near the affected joint are seen.
 - Joints have a characteristic anvil shape with an irregular flattening of central articular surface and a splaying of lateral bone.
 - TMJ involvement: Usually bilateral and occurs late in the disease:
 - Stiffness, crepitation, tenderness or limitation of mouth opening.
 - Swelling is less obvious than other joints.
 - Pain will be present due to pressure on the joint. Clenching of teeth on one side produces pain of the contralateral joint.
 - Rheumatoid arthritis in children *(Still's disease):* When it involves the TMJ, it may cause mal occlusion of class II division I type with protrusion of maxillary incisors and an anterior open bite.

Radiographic features

TMJ demonstrates a flattened condylar head with irregular surface features, an irregular temporal fossa surface and anterior displacement of the condyle.

Histopathology

- Early cases demonstrate hyperplasia of the synovial lining cells with deeper portions of the membrane showing hyperaemia, oedema and infiltration by lymphocytes, macrophages and neutrophils.
- Neutrophils are predominantly seen in synovial fluid.
- Older lesions show pronounced synovial proliferation and oedema with cholesterol crystals and fewer inflammatory cells.
- Membrane protrudes into the joint space as villi or finger-like projections.

These projections occasionally undergo necrosis producing *rice bodies* (small whitish villi fragments composed of cellular debris admixed with fibrin and collagen).

- Severely involved TMJ shows perforation of meniscus or replaced completely by fibrous scar.
- *Rheumatoid nodule:* Moderately well-demarcated area of amorphous, eosinophilic necrosis surrounded by a thick layer on mononuclear cells. The mononuclear cells closest to the amorphous centre are large and palisaded. Neutrophils are frequently seen in the centre.

Diagnosis

- Elevated rheumatoid factor (RF), an autoantibody directed toward an altered host IgG antibody.
- Antinuclear antibodies (ANAs) can be detected.
- Elevated ESR.
- Mild anaemia.

Prognosis and predictive factors

- There is no specific treatment for rheumatoid arthritis, although remarkable benefit may be seen from the administration of ACTH or cortisone.
- Once limitation of motion and deformity have occurred, surgical intervention in the form of condylectomy may be necessary to regain movement. There is, however, a great tendency for recurrence of the ankylosis.

Key points

- *Blue sclera:* Osteogenesis imperfecta, osteopetrosis, fetal rickets, Paget's disease, Marfan syndrome, Turner's syndrome and Ehlers–Danlos syndrome.
- *Marfan syndrome:* Arachnodactyly, aortic aneurysms, kyphosis and scoliosis, long and narrow skull, hyperextensibility of joints and mitral valve prolapsed.
- *Osteopetrosis* is characterized by a marked increase in bone density due to defect in normal osteoclasts function.
- *Osteoporosis* is characterized by porous bone and reduced bone mass.
- *Paget's disease* is marked by repeated episodes of increased bone

resorption followed by excessive attempts at repair, resulting in weakened, deformed bones of increased mass.

- *Polyostotic Paget's disease:* Serum alkaline phosphatase level, 250 Bodansky units.
- *Monostotic Paget's disease:* Serum alkaline phosphatase level, 50 Bodansky units.
- *Cherubism* is an autosomal dominant fibro-osseous lesion of the jaws involving more than one quadrant that stabilizes after the growth period, usually leaving with some facial deformity and malocclusion.
- *Apert syndrome* is an autosomal dominant disorder characterized by craniosynostosis, craniofacial anomalies and severe symmetric syndactyly of hands and feet.
- *Pierre Robin syndrome:* Retrognathia, glossoptosis, respiratory obstruction and cleft palate.
- *Chondroectodermal dysplasia* is an inherited skeletal disorder characterized by chondrodysplasia, ectodermal dysplasia and polydactyly with congenital heart defects.
- *Cleidocranial dysplasia* is characterized by defective development of the cranial bones and by the complete or partial absence of the clavicles.
- *Fibrous dysplasia* is a benign, self-limiting but non-encapsulated lesion showing replacement of the normal bone by a cellular fibrous tissue containing islands or trabeculae of metaplastic bone.
- Focal cemento-osseous dysplasia is a non-neoplastic lesion affecting the periapical tissues of one or more teeth.
- Florid cemento-osseous dysplasia is a lobulated mass of dense, highly mineralized, almost acellular cemento-osseous tissue typically occurring in several parts of the jaws.

Frequently asked questions

1. Osteogenesis imperfecta.
2. Marfan syndrome.
3. Marble bone disease.
4. Osteoporosis.
5. Write about pathogenesis, clinical features and histopathology of Paget's disease/jigsaw puzzle or mosaic bone pattern.
6. Cherubism.
7. Crouzon syndrome.

8. Treacher–Collins syndrome.
9. Cleidocranial dysplasia.
10. Down syndrome/Trisomy 21 syndrome.
11. Fibro-osseous lesions of jaws.
12. Discuss pathogenesis, clinical features and histopathology of fibrous dysplasia.

CHAPTER 17

Diseases of the skin

Genodermatoses

Genodermatoses are hereditary skin disorders with oral manifestations caused due to genetic defects. Many of them are accompanied by various systemic manifestations of different altered enzyme functions. Genodermatoses are characterized by alterations in the normal keratinization process, *genokeratoses.*

Ectodermal dysplasia (ED)

Ectodermal dysplasias are a heterogenous group of more than 150 syndromes, characterized by congenital dysplasia of two or more ectodermal structures and their appendages such as the hair, teeth, nails, sweat glands, salivary glands, sebaceous glands, etc.

Pathogenesis

Genetic mutations that are inherited as autosomal dominant, autosomal recessive and X-linked traits.

Clinical features

- **Gender.** Male predilection.
- **Signs and symptoms**
 - *First symptom of the disease:* Infants develop unexplained fever with elevation of temperature because of complete absence of sweat glands.
 - Sebaceous glands and hair follicles are defective or absent.
 - Hair may be thin, sparse, and very light in colour, and sparse on scalp and eyebrows.
 - Nails may be thick, abnormal-shaped, discoloured, ridged, slow-growing or brittle. The cuticles may be prone to infections.
 - Skin is soft, smooth, thin, dry, hypopigmented and more prone to infections.
 - Partial or complete absence of sweat glands; patients suffer from hyperpyrexia.
 - Bridge of the nose is depressed.
 - Supraorbital ridges and frontal bosses are pronounced.
 - Lips are protuberant.
 - ***Oral manifestations***
 - Anodontia or oligodontia

- Malformations of teeth in both deciduous and permanent dentitions
- Peg-shaped or pointed teeth
- High palatal arch and cleft palate

Hidrotic ectodermal dysplasia

(Synonym: Clouston's syndrome)
It is an autosomal dominant disorder.

Clinical features

- Nail dystrophy associated with hair defects and palmoplantar dyskeratosis. Nails are thickened and discoloured.
- Scalp hair is very sparse, fine and brittle.
- Eyebrows are thinned or absent.
- Patients have normal facies, normal sweating and no specific dental defect is seen.

Hypohidrotic (anhidrotic) ectodermal dysplasia

(Synonym: Christ–Siemens–Touraine syndrome)

- It is usually inherited as X-linked recessive trait, autosomal recessive and autosomal dominant forms.
- *Face:* Frontal bossing, sunken cheeks, saddle nose, thick and everted lips, wrinkled hyperpigmented skin around the eyes and large low set ears are seen.
- Hypohidrosis, anomalous dentition, onychodysplasia, and hypotrichosis are also present.
- *Oral manifestations:* Conical or peg-shaped teeth, hypodontia or complete anodontia and delayed eruption of permanent teeth.
- *Others:* Short stature, eye abnormalities, decreased flow of tears and photophobia.

Histopathology

- Skin histopathology shows that reduction in number of sweat glands, hair follicles and sebaceous glands.
- In hypohidrotic ectodermal dysplasia, epidermis is thin and flattened.
- Eccrine sweat glands are few or poorly developed or rudimentary.
- Mucous glands in the upper respiratory tract and bronchi are reduced in number.

- Salivary gland may show ectasia of ducts and inflammatory changes.

Prognosis and predictive factors

- Cosmetic dental treatment.
- Multiple denture replacements as the child grows.
- Implants may be an option in adolescence, once the jaw is fully grown.
- Orthodontic treatment for malocclusion.

Chondroectodermal dysplasia

(Synonym: Ellis–van Creveld syndrome)
Chondroectodermal dysplasia (CED) is a rare genetic disorder with an autosomal recessive pattern of inheritance causing multiple skeletal anomalies.

Pathogenesis

- It is an autosomal recessive disorder.
- The locus gene mapped to chromosome 4p16.1.
- It affects both mesodermal and ectodermal tissues.

Clinical features

- A clinical tetrad of Ellis–van Creveld syndrome consists of chondrodystrophy, polydactyly, ectodermal dysplasia, and cardiac anomalies.
- Nails are hypoplastic with koilonychias.
- Sweating will be normal.
- Arms and legs are shortened and thickened.
- The bilateral polydactyly affects the hands and occasionally the feet.
- ***Oral manifestations***
 - Upper lip has a slight V-shaped notch in the middle due to the fusion of the anterior portion of the upper lip to the maxillary gingival margin, resulting in an absence of mucobuccal fold.
 - Short upper lip is bound by frenula to alveolar ridge (lip tie).
 - Often serrated lower alveolar ridge.
 - Congenitally missing teeth.
 - Premature eruption (at birth) and premature exfoliation of teeth.

Prognosis and predictive factors

- The care for respiratory distress, recurrent respiratory infections, and cardiac failure is supportive.
- Dental care in childhood includes:
 - Neonatal teeth should be extracted as they may impair feeding.
 - Prevention of caries includes dietary counselling, plaque control, and oral hygiene instruction.
 - Crown or composite build-ups for microdonts may be indicated.
 - Partial dentures can maintain space and improve mastication, aesthetics, and speech due to congenitally missing teeth.
- During adulthood, implants and prosthetic rehabilitation are required to replace congenitally missing teeth.

Ehlers–Danlos syndrome

(Synonyms: Tenascin X deficiency syndrome; lysyl hydroxylase deficiency syndrome; cutis hyperelastica)

Ehlers–Danlos syndrome (EDS) is a group of inherited connective tissue disorders, caused by a defect in the synthesis of collagen (type I or III).

Pathogenesis

- Mutations in *COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2* and *TNXB* genes.
- Mutations in these genes usually alter the structure, production, or processing of collagen or proteins that interact with collagen. A defect in collagen can weaken connective tissue in the skin, bones, blood vessels, and organs, resulting in the features of the disorder.

Clinical features

- The classic signs of EDS are joint hypermobility, hyperelasticity of skin, which is soft, thin and fragile; the presence of dystrophic scars; and a tendency to excessive bleeding manifested by bruises, ecchymoses and haematomas.
- Scarring of skin following wound healing is unusual. Scar tends to spread rather contract, *papyraceous scarring*, because it resembles crumpled cigarette paper.
- The extraoral manifestations include presence of scarring on the chin and

forehead, a history of repeated luxations of the TMJ, epicanthus, hypertelorism, a narrow curved nose, sparse hair and hyperelasticity of the skin.

- The oral mucosa is as fragile as the skin; it tears easily when touched by instruments. Sutures do not hold.
- Patients can touch tip of their nose with their tongue—*Gorlin's sign.*
- The fragility of the gingiva can be detected following treatments such as prophylaxis, periodontal surgery or extraction. Haemorrhage may be difficult to control during surgical procedures.
- Early onset of generalized periodontitis is one of the most significant oral manifestations of the syndrome. This can lead to the premature loss of deciduous and permanent teeth.
- High and narrow palate results in crowding of teeth.
- Hypoplasia of the enamel is commonly seen. Premolar and molar teeth can present with deep fissures and long cusps. The teeth seem to be brittle and microdontia is sometimes present.
- Radiographic examination often reveals pulp stones and roots that are short and deformed.

Histopathology

- Lack of normal scalloping in dentinoenamel junction is seen.
- Passage of many dentinal tubules into enamel and formation of much irregular dentine are seen.
- Increased tendency of large pulp stones is present.

Prognosis and predictive factors

- There is no cure for Ehlers–Danlos syndrome. The treatment is supportive.
- The presence of mitral valve prolapse generally indicates that prophylactic antibiotics are indicated for relevant dental procedures.
- Dental visits of short duration are preferable in order to avoid causing iatrogenic problems.
- Ideally, dental and maxillofacial surgery should be avoided. It is imperative to test blood coagulation values before proceeding with surgery. Sutures, which do not hold well, should be covered with acrylic dressings.

Focal dermal hypoplasia syndrome/Goltz–Gorlin syndrome

(Synonyms: Goltz syndrome; Goltz–Gorlin syndrome)

- Focal dermal hypoplasia (FDH) is an uncommon genetic disorder characterized by distinctive skin abnormalities and a wide variety of defects that affect the eyes, teeth, skeletal, urinary, gastrointestinal, cardiovascular, and central nervous systems.
- The name is a misnomer, as the skin manifestations appear as a result of lipid accumulation rather than hypoplasia of dermis.
- It is usually, but not always, X-linked dominant disease.
- FDH is also known as *Goltz–Gorlin syndrome*. It should not be confused with Gorlin–Goltz syndrome which is a *naevoid basal cell carcinoma syndrome*.

Pathogenesis

Focal dermal hypoplasia is a genetic defect that has been associated with at least 24 different mutations in the *PORCN* gene mapped to locus Xp11.23.

Clinical features

- The affected individuals are recognized at birth or often prenatally.
- It occurs predominantly in females.
- Facial abnormalities include asymmetry of the face with mild hemiatrophy, pointed chin, sparse eyebrows and eyelashes, low set ears, narrowed nasal bridge and a broad nasal tip with a unilateral notch of the nasal alae.
- ***Oral manifestations***
 - Mandibular prognathism
 - Agenesis or dysplasia of the teeth
 - Delayed tooth formation/eruption
 - Microdontia
 - Irregular spacing and malocclusion
 - Enamel hypoplasia, and notching of the incisors
 - High-arched palate
 - Double lingual frenula
 - Cleft lip and cleft palate
 - Absence of a labial sulcus
 - Gingival hyperplasia

- Taurodontism
- Papillomas of the gingiva, tongue, palate, and buccal mucosa.

Histopathology

The dermis may be totally or partially replaced by accumulation of adipose cells, which appear as striking hernia-like outpouchings of fatty tissue; this feature is unique to focal dermal hypoplasia.

Prognosis and predictive factors

Management of focal dermal hypoplasia is targeted towards the various soft tissue, dental, and skeletal anomalies, with the goal of achieving optimal functional and aesthetic results.

White sponge naevus

(Synonyms: Cannon's disease; hereditary leukokeratosis of mucosa)
First described by Cannon in 1935, white sponge naevus (WSN) is a rare genodermatosis that is inherited as an autosomal dominant trait.

Pathogenesis

Defect in normal keratinization of the oral mucosa due to mutations of the keratin 4 or keratin 13 genes, located on 12q13 and 17q21.

Clinical features

- **Age.** Appear at birth or early childhood.
- **Sex.** No sex predilection.
- **Location.** Buccal mucosa, ventral tongue, labial mucosa, soft palate, alveolar mucosa, and floor of the mouth.
- **Signs and symptoms**
 - Symmetric, thickened, white, corrugated or velvety, diffuse plaques affect bilaterally.
 - Usually asymptomatic, rare examples of mild discomfort have been reported from secondary infection.
 - Lesions are usually well demarcated from the surrounding normal mucosa, as opposed to the poor demarcation of leukoedema and smokeless tobacco keratosis.
 - It does not disappear when the affected mucosa is stretched.

Histopathology

- Prominent hyperkeratosis and marked acanthosis with clear cytoplasm of spinous cells are seen.
- Eosinophilic condensation in the perinuclear region of the cells in the superficial layers of the epithelium is a unique feature to white spongy naevus.
- Ultrastructural view shows tangled masses of keratin tonofilaments.

Differential diagnosis

- Leukoedema
- Frictional keratosis
- Leukoplakia

Prognosis and predictive factors

- The occasional mildly symptomatic cases respond to topical applications of tetracycline.
- There is no malignant potential and it does not interfere with normal masticatory functions, and so no treatment is required except for the rare example of a plaque which extends on to the lip vermilion and is surgically removed for aesthetic reasons.

Pachyonychia congenita

(Synonym: Polykeratosis congenita)

Pachyonychia congenita (PC) is a rare genodermatosis characterized by dystrophic, thickened nails, focal palmoplantar keratoderma and oral leukokeratosis.

Pathogenesis

Autosomal dominant mutations in the genes encode epidermal keratins—K6a, K6b, K16 and K17.

Types

- *PC type 1, or the Jadassohn–Lewandowsky type:* Congenital onset, hypertrophic nail dystrophy, palmoplantar keratoderma and hyperhidrosis, follicular hyperkeratosis and oral leukokeratosis.
- *PC type 2, or the Jackson–Lawler type:* Congenital onset, natal teeth,

steatocystomas, and pili torti (twisted hair).

- *PC type 3 or PC tarda:* Onset ranges from late childhood to middle age.

Clinical features

- **Age.** Appear at birth or early childhood.
- **Sex.** No sex predilection.
- **Location.** Nails, skin, hairs, buccal mucosa, lateral and dorsal margins of tongue, alveolar mucosa and palate.
- **Signs and symptoms**
 - *Nail changes:* The free margins of nails are lifted up because of an accumulation of keratinaceous material in the nail beds. This results in a pinched, tubular configuration. Ultimately, nail loss may occur.
 - *Skin changes:* The palmoplantar keratoderma is symmetric and focal, developing particularly in areas of friction, trauma, and weight bearing. Follicular hyperkeratosisis frequently found on the elbows, knees and waist band areas.
 - Sometimes sparse hair and corneal dyskeratosis producing corneal opacities are reported.
 - ***Oral manifestations***
 - Leukokeratosis of the oral mucosa is a prominent sign of PC type 1. Patchy hyperkeratotic areas are most commonly seen on the tongue and buccal mucosa. The gingival mucosa is rarely involved. The clinical appearance of the lingual and buccal leukokeratoses can resemble candidiasis and leukoplakia. In newborns, the leukokeratoses may lead to difficulties in suckling and breastfeeding.
 - Natal or neonatal teeth are associated with PC type 2 and are present at birth or within the first 30 days of life. They are typically lost in infancy and replaced with permanent teeth. Natal teeth may lead to trauma or lacerations of the infant's tongue or mother's breast during breastfeeding and can pose an aspiration risk in infancy.

Histopathology

Lesional oral mucosa shows marked hyperparakeratosis and acanthosis with perinuclear clearing of epithelial cells.

Differential diagnosis

- Leukoplakia

- Dyskeratosis congenita
- White spongy naevus

Prognosis and predictive factors

- Like most genodermatoses, no specific treatment or cure is known for PC.
- Symptomatic treatment: Mechanical thinning of keratotic nails and calluses, systemic retinoids, topical anaesthetics for blisters and surgical excision of cysts.

Dyskeratosis congenita

(Synonyms: Zinsser–Engman–Cole syndrome; Hoyeraal–Hreidarsson syndrome)

- Dyskeratosis congenita (DKC) is an inherited bone marrow failure syndrome that is characterized by reticular hyperpigmentation of the skin, dystrophic nails, mucous membrane leukoplakia and pancytopenia.
- Patients have an increased prevalence of malignant mucosal neoplasms in DKC.

Pathogenesis

- Reduction in telomerase RNA component (TERC) levels invariably affecting the normal function of telomerase which maintains these telomerase.
- Though the exact pathophysiology of the disease is not yet fully understood, most evidences point to DKC being primarily a disorder of poor telomere maintenance.

Clinical features

- **Age.** It appears at birth or early childhood.
- **Sex.** Male predilection.
- **Location.** Nails, skin, hairs, buccal mucosa, lateral and dorsal margins of tongue and palate.
- **Signs and symptoms**
 - Nail changes are usually the first manifestation of disease, which becomes dystrophic and shedding some time after the age of 5 years.
 - Greyish-brown skin pigmentation appears at same time or few years later over trunk, neck and thighs.
 - DKC is a multi-system disorder in which affected patients often develop

pancytopenia, abnormalities of the eye, lacrimal duct stenosis, pulmonary fibrosis and malignancy, in addition to changes of skin and mucosa.

- *Oral manifestations*
 - Leukoplakia occurs in approximately 80% of cases and particularly in young patients with no history of tobacco usage. Typically involves the buccal mucosa, tongue and oropharynx. The leukoplakia may become verrucous and ulcerated.
 - Increased frequency of dental caries
 - Hypodontia
 - Thin enamel structure
 - Aggressive periodontitis
 - Intraoral brown pigmentation
 - Taurodontism
 - Multiple permanent teeth with decreased root/crown ratios.

Increased risk of malignancy

- Patients have an increased prevalence of malignant mucosal neoplasms, particularly squamous cell carcinoma of the mouth, nasopharynx, oesophagus, rectum, vagina or cervix. These often occur within the sites of leukoplakia.
- The prevalence of squamous cell carcinoma of the skin is also increased.
- Other malignancies reported include Hodgkin's lymphoma, adenocarcinoma of the gastrointestinal tract, and bronchial and laryngeal carcinoma.
- Malignancy tends to develop usually in the third decade of life.

Histopathology

- Skin lesions show mild hyperkeratosis, epidermal atrophy, telangiectasia of superficial blood vessels and melanophages in papillary dermis.
- Oral leukoplakic lesions appear to be nonspecific hyperparakeratosis or hyperorthokeratosis and acanthosis.

Differential diagnosis

- Pachyonychia congenita
- White spongy naevus
- Leukoplakia

Prognosis and predictive factors

- Like most genodermatoses, no specific treatment or cure is known.
- Symptomatic treatment.

Keratosis follicularis

(Synonyms: Darier disease; dyskeratosis follicularis)
Darier disease is a rare genodermatosis characterized by hyperkeratotic papules in seborrhoeic regions, nail abnormalities and mucous membrane changes.

Pathogenesis

- The cause has been traced to chromosome 12, where a spectrum of mutations is noticed within the *ATP2A2* gene encoding the calcium ATPase of the sarco-endoplasmic reticulum (SERCA2) resulting in abnormal organization or maturation of complexes responsible for cell adhesion, thus leading to the abnormal cell-to-cell adhesion and aberrant maturation in keratinocytes.
- The pattern of inheritance is autosomal dominant.

Clinical features

- **Age.** 6–20 years.
- **Sex.** Male predilection.
- **Location.** Forehead, scalp, margin of the scalp, nasolabial folds, ears, chest and back.
- **Signs and symptoms**
 - Yellow-brown papules with a greasy, warty texture in seborrhoeic areas are seen.
 - Scattered papules with malodour in the groin or axillae, or submammary skin in women are seen.
 - Punctate keratoses, palmar pits and haemorrhagic macules are seen on palms.
 - It is exacerbated by ultraviolet light exposure, heat, humidity and friction.
 - White and red longitudinal bands, longitudinal nail ridges, longitudinal splitting and subungual hyperkeratosis and V-shaped nick at the free margin of the nails are seen.

- *Oral manifestations*
 - Site: Gingiva, tongue, hard and soft palate, buccal mucosa, sometimes pharynx and larynx.
 - It consists of multiple, normal coloured or white flat-topped papules with a central depression which occur on the buccal mucosae, palate and gingiva with a *cobblestone* appearance.

Histopathology

- Acantholysis and dyskeratosis (abnormal premature keratinization) are the two main features seen.
- Acantholysis frequently results in the formation of characteristic suprabasal clefts.
- The underlying rete pegs, covered by a single layer stratum basale, project into these clefts and form villus-like structures. A large keratin plug, often showing focal parakeratosis, overlies each lesion.
- Hyperkeratosis is also common.
- There are two types of dyskeratotic cells: (i) corps ronds and (ii) grains.
 - *Corps ronds* are predominantly located in the stratum spinosum and the stratum granulosum. Corps ronds are characterized by an irregular eccentric and sometimes pyknotic nucleus, a clear perinuclear halo and a brightly eosinophilic cytoplasm.
 - *Grains* are mostly located in the stratum corneum, and they consist of oval cells with elongated cigar-shaped nuclei and abundant keratohyalin granules.

Differential diagnosis

- Familial benign pemphigus (Hailey–Hailey disease)
- Seborrhoeic dermatitis
- Transient acantholytic dermatosis

Prognosis and predictive factors

- Topical retinoids
- Surgical treatment includes dermabrasion, carbon dioxide laser and erbium YAG laser.

Acanthosis nigricans

- Acanthosis nigricans (AN) is a skin disorder characterized by hyperpigmentation and hyperkeratosis of the skin, occurring mainly in the folds of the skin in the axilla, groin and back of the neck.
- It is not a skin disease per se but a cutaneous sign of an underlying disease.
- It typically occurs in individuals younger than 40 years, may be genetically inherited, and is associated with obesity or endocrinopathies, such as hypo- or hyperthyroidism, acromegaly, polycystic ovary disease, insulin-resistant diabetes or Cushing's disease. The most common cause of AN is insulin resistance, which leads to increased circulating insulin levels.
- There are two important types of AN—benign and malignant. Although classically described as a sign of internal malignancy, this is very rare. Benign types, sometimes described as 'pseudoacanthosis nigricans', are much more common.
- Thickened brown velvety textured patches of skin that may occur in any location but most commonly appear in the folds of the skin in the armpit, groin and back of the neck.
- Papillomatosis is common on cutaneous and mucosal surfaces.
- Skin tags often found in and around affected areas.
- Pruritus may be present.
- Lesions may also appear on the mucous membranes of the oral cavity, nasal and laryngeal mucosa and oesophagus.
- Lesions involving the mucosa, palms and soles tend to be more extensive and more severe in malignant AN.
- Patients with malignant AN tend to be middle-aged, not obese and lesions develop abruptly.
- If the underlying cause can be determined and treated appropriately, the disease fades.
- People with AN should be screened for diabetes and although rare, cancer. Controlling blood glucose levels through exercise and diet often improves symptoms. Acanthosis nigricans maligna may resolve if the causative tumour is successfully removed.

Direct immunofluorescence/indirect immunofluorescence

Two immunofluorescence techniques are widely used to investigate the autoimmune vesiculobullous diseases:

1. Direct immunofluorescence
2. Indirect immunofluorescence

Direct immunofluorescence (fig. 17.1)

- It is used to detect autoantibodies that are bound to the patient's tissue.
- Inoculate human immunoglobulins into a goat, it creates antibodies directed against these human immunoglobulins.
- The antibodies raised in response to human immunoglobulins are harvested from the animal and tagged with fluorescein, a dye that glows when viewed with UV light.
- A frozen section of the patient's tissue is placed on a slide and it is incubated with fluorescein conjugated goat antihuman antibodies.
- These antibodies bind to the tissue at any site where human immunoglobulin is present.
- The section is then viewed with a UV light source microscope.

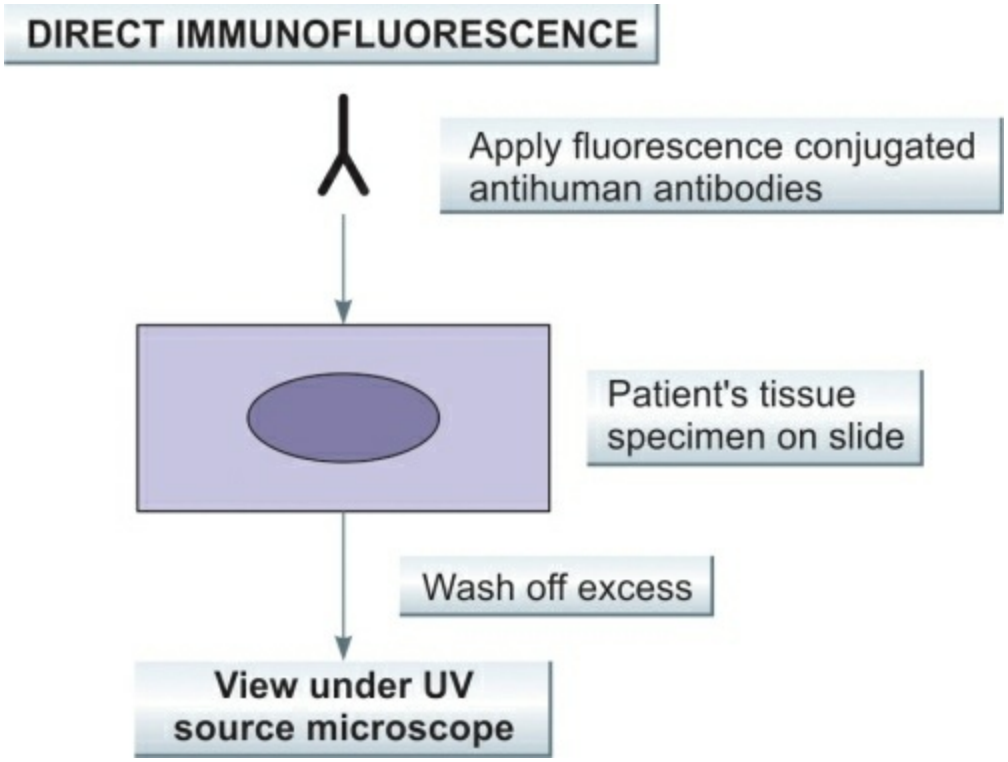


FIG. 17.1 Direct immunofluorescence technique.

Indirect immunofluorescence (fig. 17.2)

- The patient is being evaluated for presence of antibodies that are circulating in blood.
- A frozen section of tissue which is similar to human oral mucosa (monkey's mucosa) is placed on a slide and incubated with the patient's serum.
- If autoantibodies directed against epithelial attachment structure are present in the patient's serum, then they will attach to homologous structures on the tissue.
- Then fluorescein conjugated goat antihuman antibody is incubated with the section.
- The excess is washed off and the section is examined with UV light source microscope to detect the presence of autoantibodies that might have been in serum.

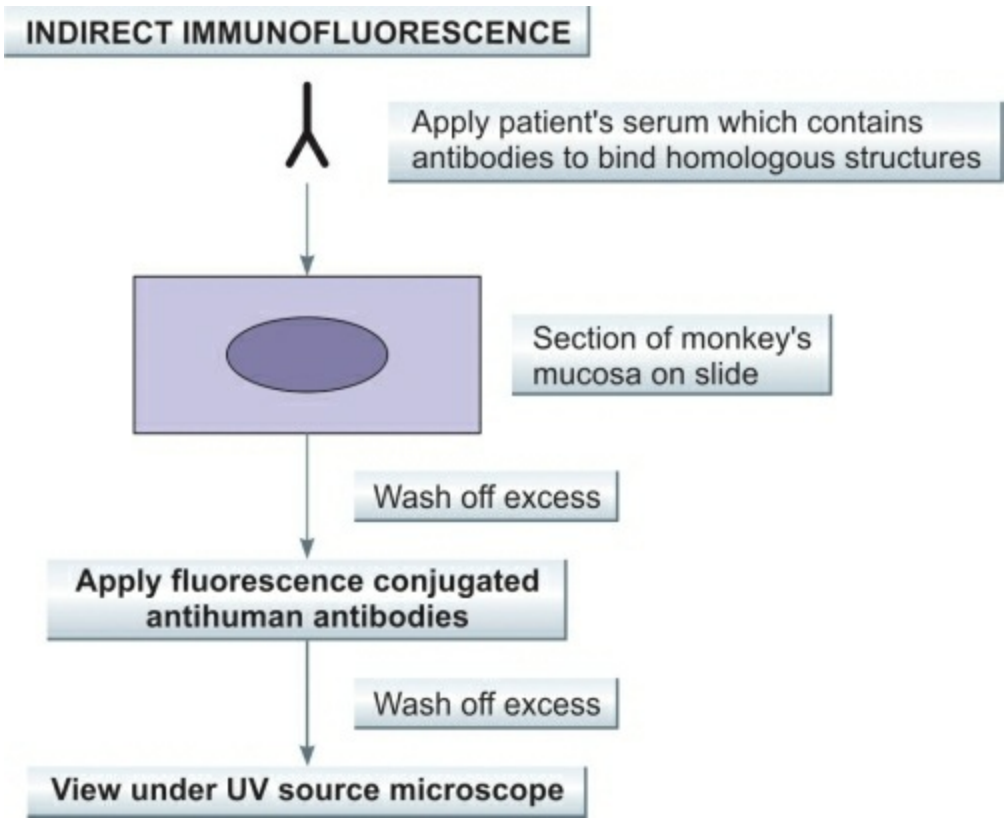


FIG. 17.2 Indirect immunofluorescence technique.

Lichen planus

(Synonym: Lichen ruber planus)

- Lichen planus (LP) is a common immunologically mediated mucocutaneous disease.
- It was first described by Erasmus Wilson in 1869.
- The term *Lichens* means *primitive plants composed of symbiotic algae and fungi* and *planus* means *flat*. Since the lesions were flat topped papules resembling the algae growing on rocks, Erasmus Wilson called them *lichen planus*.

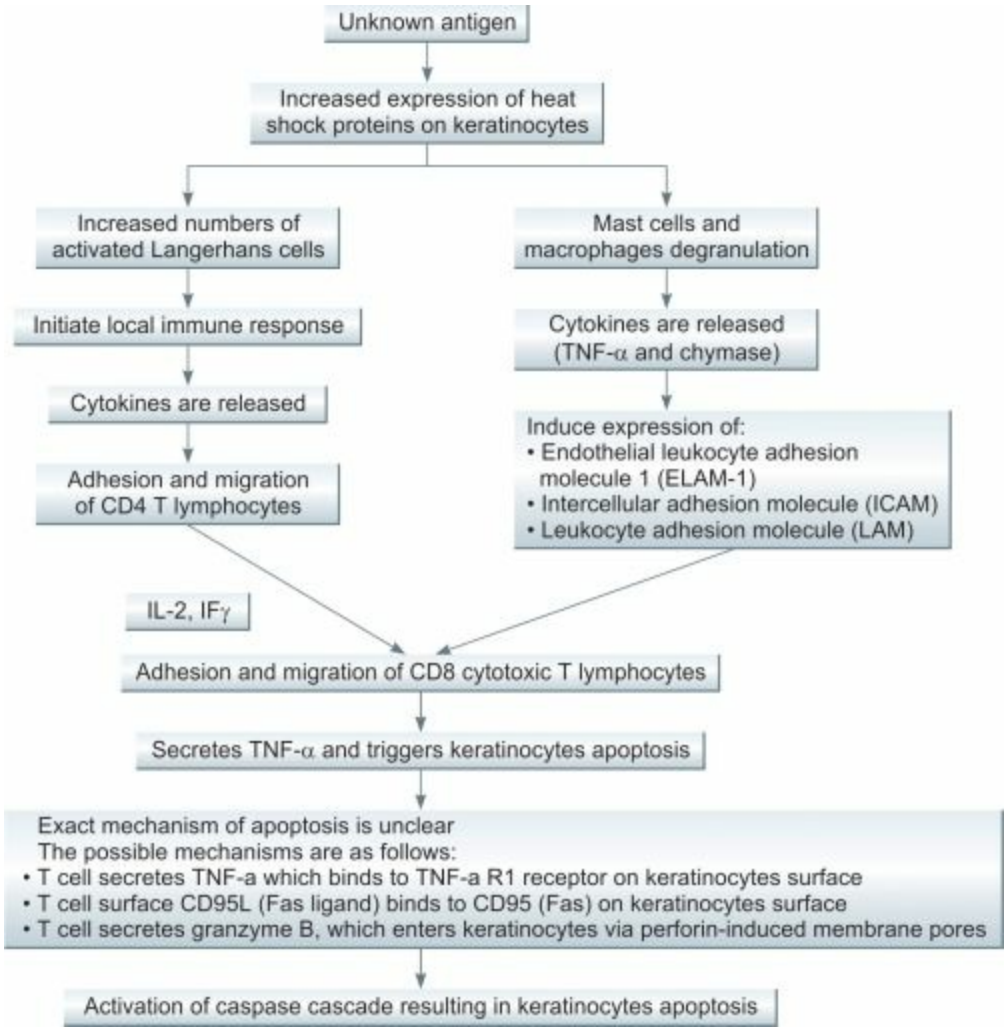
Pathogenesis

Aetiology

- Drugs: Antimalarials, NSAIDs, angiotensin converting enzyme inhibitors, diuretics, β-blockers
- Dental materials: Dental amalgam, composite and resin-based materials and metals
- Chronic liver disease and hepatitis C virus
- Stress
- Genetics
- Tobacco chewing
- Graft-versus-host disease
- Mechanical trauma *(Koebner phenomenon)*

The course of the disease is long from several months to years, frequently undergoes periods of remission followed by exacerbations by emotional upset, overwork, anxiety, mental strain, trauma, malnutrition and infections.

Pathogenesis of oral lichen planus is illustrated in Flowchart 17.1.



FLOWCHART 17.1 Pathogenesis of oral lichen planus

An interesting association between lichen planus, hypertension and diabetes mellitus is described as *Grinspan syndrome*. However, this association is thought to be coincidental as drugs used in these systemic diseases may cause an *oral lichenoid reaction.*

Clinical features

- **Age.** Older age group.
- **Sex.** Female predilection.
- **Location.** Flexor surface of wrist and forearms, knees, trunk, sacral area, scalp and nails.
- **Signs and symptoms**
 - The skin lesions appear as small flat-topped papules of few millimetre in diameter.
 - These may be discrete or gradually coalesce into large plaques.

- The surface is covered by very fine greyish white lines called *Wickham's striae.*
- The primary symptom is intense pruritus; scalp and nail involvement is rare.
- Early lesion appears red—reddish purple or violaceous hue—dusky brown colour develops.
- *Oral manifestations*
 - Oral lichen planus (OLP) may occur weeks or months before the appearance of the skin lesions.
 - The most common sites include the buccal mucosa (often bilaterally), followed by the tongue, lips, gingiva, the floor of the mouth and the palate are less frequently involved.
 - Usually asymptomatic, occasionally burning sensation is the main symptom.
 - OLP is classified into six subtypes:
 1. Reticular
 2. Papillary
 3. Atrophic
 4. Erosive
 5. Bullous
 6. Plaque-like
 - *Reticular LP:* It consists of slightly elevated fine whitish lines (Wickham's striae) that produce either a lace-like pattern or a pattern of fine radiating lines or annular lesions. This is the most common and most readily recognized form of lichen planus. Most patients with lichen planus at some time exhibit some reticular areas.
 - *Papillary LP:* It consists of radiating white or grey, velvety thread-like papules in a linear, annular or retiform arrangement forming rings or streaks on the buccal mucosa, and to a lesser extent lips and tongue.
 - *Atrophic LP:* It appears clinically as smooth, red, inflamed areas of the oral mucosa covered by thinned red-appearing epithelium. When it involves the gingiva, it results in desquamative gingivitis.
 - *Erosive LP:* It probably develops as a complication of the atrophic process when the thin epithelium is abraded or ulcerated. These lesions are invariably symptomatic, with symptoms that range from mild burning to severe pain.
 - *Bullous LP:* It is rare and clinical presentation is nonspecific as the bulla immediately bursts to form an ulcer. Often diagnosed on

histopathological findings.

- *Plaque-like* or *hypertrophic LP:* It is well-circumscribed, elevated, white lesion resembling a leukoplakia. In such cases, biopsy is helpful in diagnosis.

Histopathology (fig. 17.3)

- Areas of hyperparakeratosis or hyperorthokeratosis, often with a thickening of the granular cell layer.
- Acanthosis.
- Saw-tooth rete pegs.
- Liquefaction degeneration of the basal cell layer
- Detachments between epidermis and dermis may be present (Max–Joseph spaces).
- Round, eosinophilic globules (Civatte bodies/hyaline bodies/Sabouraud's bodies/colloid bodies), representing degenerated epithelial cells or phagocytosed epithelial cell remnants within macrophages are often scattered within the epithelium and superficial lamina propria. These represent cells that have undergone apoptosis.
- Dense subepithelial band of lymphocytic infiltrate is confined to lamina propria.
- Atrophic type shows atrophic epithelium.
- Erosive type shows area of erosion/ulcer covered by pseudomembrane.
- Direct immunofluorescence shows deposition of a shaggy band of fibrinogen at the basement membrane zone.

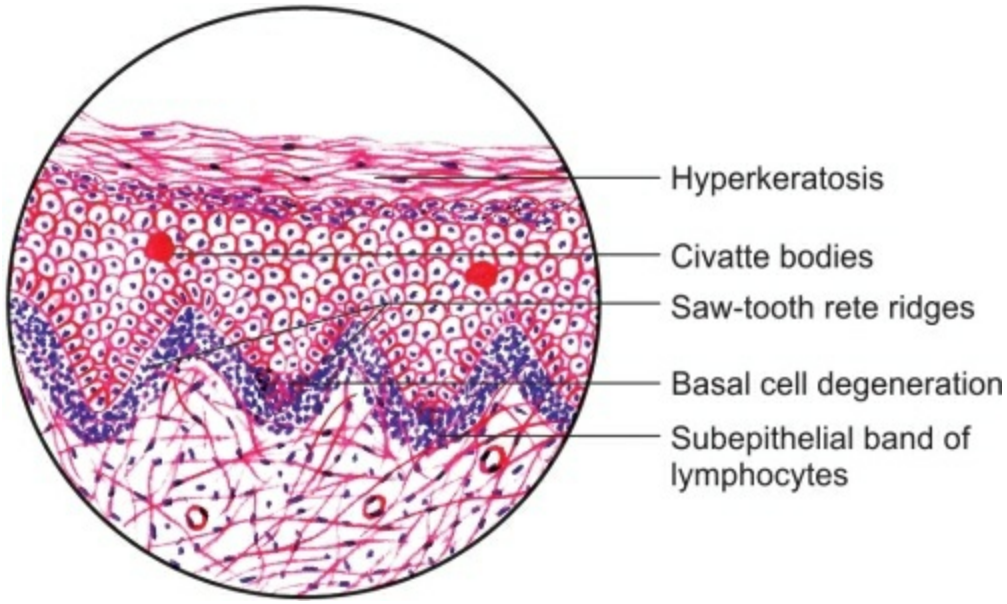


FIG. 17.3 Oral lichen planus.

Differential diagnosis

- Lichenoid reactions (e.g. drug-induced lesions, contact mercury hypersensitivity)
- Lupus erythematosus
- Graft-versus-host reaction

Prognosis and predictive factors

- There is no known cure for OLP; therefore, the management of symptoms guides therapeutic approaches.
- Corticosteroids have been the most predictable and successful medications for controlling signs and symptoms.
- The most commonly used are 0.05% fluocinonide and 0.05% clobetasol. These are frequently prescribed as pastes or gels.
- Ulcerative/erosive and atrophic types are known to undergo malignant transformation.

Psoriasis

Psoriasis is a noncontagious skin disorder which appears as inflamed oedematous skin lesions covered with silvery-white scales.

Pathogenesis

- The aetiology is multifactorial, but it has a strong hereditary component and it has been related to certain trigger factors such as streptococcal infections, tobacco smoking, alcohol consumption, stress, obesity, as well as certain drugs as beta-blockers, lithium carbonate, nonsteroidal anti-inflammatory agents, systemic corticosteroids and other therapeutic agents.
- Genetic predisposition: This disease has strong association with HLA-Cw6 and HLA-B57 regions. Other gene loci such as 19p13, 17q25 and 1q21 may also increase susceptibility to disease.
- Autoimmune disease: Psoriasis is associated with increased activity of T cells in underlying skin.
- Lesions are due to increased turnover rate of dermal cells, from the normal turnover duration of 2–3 days to 3–5 days in affected areas. There is also a dramatic increase in mitotic index of psoriatic skin, which is more than epidermoid carcinoma.

Clinical features

- **Age.** 20–30 years.
- **Sex.** Female predilection.
- **Location.** Skin of the elbows and knees, scalp, palms and soles.
- **Signs and symptoms**
 - There are five types of psoriasis: (i) plaque, (ii) guttate, (iii) inverse, (iv) pustular and (v) erythrodermic. The most common form is plaque psoriasis, which is commonly seen as silvery-white plaques.
 - The disorder is a chronic recurring condition that varies in severity from minor localized patches to complete body coverage.
 - These small papules, which are roughly symmetrical, coalesce to form large plaques of irregular outline on extensor surfaces of extremities.
 - Psoriatic nail dystrophy and psoriatic arthritis are common.
 - Gentle scraping of the surface of a psoriasis plaque with a glass slide will remove the loosely attached scales and reveal a shiny surface peppered with fine bleeding points. These bleeding points represent the dilated and tortuous capillary blood vessels in the papillary dermis, one of the characteristic pathological events taking place in psoriasis affected skin. This sign is known as *Auspitz sign*, which is a diagnostic sign of psoriasis and is named after Heinrich Auspitz.
 - The cutaneous lesions are painless and seldom pruritic, may be few in number or extensive in distribution.

- The disease is more severe in winter and less severe in summer due to increase exposure to UV light. When the patient moves to a sunny climate, the condition usually shows improvement.
- *Oral manifestations*
 - Site: Lips, buccal mucosa, palate, gingiva and floor of the mouth.
 - Clinical forms include:
 – Grey or yellowish-white plaques
 – Silvery-white, scaly lesion with erythematous base
 – Multiple popular eruptions which may ulcerate
 – Small, papillary, elevated lesions with a scaly surface
 - The migratory stomatitis in the oral cavity and the geographic tongue, which is confined to the dorsal and lateral aspects of the tongue mucosa, are believed to be oral manifestations of psoriasis, as being histologically identical to cutaneous psoriasis lesions and more prevalent among psoriasis patients.

Histopathology

- Uniform parakeratosis, absence of a stratum granulosum, and elongated and clubbing rete ridges are usually seen.
- The overlying epithelium is thinned—it is from these points that bleeding occurs when scales are peeled off.
- Tortuous dilated capillaries extending high in the papillae are prominent.
- Intraepithelial microabscesses are common—*Monro's abscesses.*
- Mild lymphocytic and histiocytic infiltration of connective tissue is seen, particularly perivascular and periadnexal in location.

Note: Histopathology of erythema migrans (geographic tongue), oral mucosal cinnamon reaction and psoriasis will be similar.

Differential diagnosis

- Seborrhoeic dermatitis
- Pityriasis rubra
- Pemphigus foliaceus

Prognosis and predictive factors

- Topical application of corticosteroids, vitamin D analogues, retinoids and salicylic acid
- Phototherapy: Sunlight, ultraviolet A (UVA), ultraviolet B (UVB) lights are used.
- Photochemotherapy or psoralen plus ultraviolet A (PUVA) is given.
- Excimer laser and pulsed dye laser can also be used.

Pityriasis rosea

- Pityriasis rosea (PR) is a common, self-limited rash that typically occurs in healthy adolescents and young adults.
- The word *pityriasis* means *fine scales* and *rosea* means *rose- or pink-coloured*.
- It may clinically resemble secondary syphilis.

Pathogenesis

- Although its cause is unknown, its clinical presentation and immunologic reactions suggest viral infection as a cause and the rash itself is associated with the following characteristics:
 - It may be preceded by a recent acute infection with fever, fatigue, headache and sore throat.
 - It occurs more often in the colder months.
 - It occurs in all races equally.
- Recent studies have found HHV-7 viral DNA in the lesions and plasma of patients with PR. However, its aetiological role is controversial as it is found even in healthy people.

Clinical features

- **Age.** Children and young adults.
- **Sex.** Female predilection.
- **Location.** Skin of the shoulders, chest, thighs and forearms.
- **Signs and symptoms**
 - A primary lesion or 'herald spot' of 3–4 cm diameter precedes the generalized outbreak by 7–10 days.
 - The rash persists for 3–6 weeks and seldom recurs.
 - Mild itching will be present.
 - *Oral manifestations*
 - Site: Buccal mucosa, tongue and palate.
 - Erythematous macules with or without central area of greyish

desquamation.
- It occurs concomitantly with skin rashes and clear with them.
- Lesions are usually asymptomatic.
- Lesions are single or multiple, irregular in shape, often with raised borders.

Histopathology

- Acanthosis and focal parakeratosis are commonly seen.
- Oedema, hyperaemia and perivascular infiltration of lymphocytes, plasma cells and histiocytes in the connective tissue are seen.

Prognosis and predictive factors

- Topical steroids, antihistamines to relieve pruritus.
- UVB light therapy.

Erythema multiforme

Erythema multiforme (EM) is an acute, self-limited and sometimes recurring skin condition that is considered to be a type IV hypersensitivity reaction associated with certain infections, medications and various other triggers.

Pathogenesis

- **Precipitating agents**
 - Infections: Herpes simplex, *Mycoplasma pneumoniae.*
 - Drugs: Barbiturates, digitalis, penicillin, salicylates, sulphonamides (sulpha drugs).
- **Aetiology**
 - The exact cause is unknown.
 - The disorder is believed to involve damage to the blood vessels of the skin, followed by damage to skin tissues.

Classification

Erythema multiforme may be present within a wide spectrum of severity:

- *Erythema multiforme minor:* Typical targets or raised, oedematous papules distributed acrally with minimal or no involvement of mucosa.
- *Erythema multiforme major:* Typical targets or raised, oedematous papules distributed acrally with involvement of one or more mucous membranes;

epidermal detachment involves less than 10% of total body surface area (TBSA).

- *Stevens–Johnson syndrome:* Widespread blisters predominant on the trunk and face, presenting with erythematous or pruritic macules and one or more mucous membrane erosions; epidermal detachment is less than 10% TBSA for Stevens–Johnson syndrome.
- *Toxic epidermal necrolysis (TEN):* Epidermal detachment is 30% or more in TEN.

Clinical features

- **Age.** 20–30 years.
- **Sex.** Male predilection.
- **Location.** Hands, wrists, ankles and oral mucosa.
- **Signs and symptoms**
 - Acute onset and may display a wide spectrum of clinical disease.
 - Prodromal symptoms: Fever, malaise, headache, cough and sore throat. It occurs 1 week before onset. Although the disease is self-limiting, it may last for 2–6 weeks.
 - Skin lesions: A variety of appearances may be present, hence the name, *multiforme* which means *many forms.* Early lesions appear on extremities as flat, round and dusky red in hue. Later, these lesions become slightly elevated and may evolve into bullae with necrotic centres. These lesions appear as concentric circular erythematous rings resulting from varying shades of erythema resembling target or bull's eye—*Iris* or *target lesions.*
 - *Oral manifestations*
 - Sites: Lips, labial mucosa, buccal mucosa, tongue, floor of the mouth, soft palate.
 - It begins as erythematous patches that undergo epithelial necrosis and evolve into large shallow erosions and ulcerations with irregular borders.
 - The ulceration often has a diffuse distribution.
 - Haemorrhagic crusting of the vermilion zone of the lips is common.

Erythema multiforme minor

- It represents a localized eruption of the skin with minimal or no mucosal involvement.
- The papules evolve into pathognomonic target lesions or Iris lesions that

appear within a 72-hour period and begin on the extremities.
- Lesions remain in a fixed location for at least 7 days and then begin to heal.

Erythema multiforme major

- More severe erosions of at least two mucosal surfaces are seen in erythema multiforme major and are characterized by haemorrhagic crusting of the lips and ulceration of the nonkeratinized mucosa. Occasionally, painful mucosal involvement may be extensive, with few or no skin lesions.
- Mucosal lesions usually heal without sequelae. Generalized lymphadenopathy often accompanies erythema multiforme major.

Stevens–Johnson syndrome (SJS)

- At one time, it was considered as a separate disease, but now it is recognized as a very severe bullous form of erythema multiforme with widespread involvement typically including the skin, oral cavity, eyes and genitalia.
- It commences with abrupt occurrence of fever, malaise, photophobia and eruptions of the oral mucosa, genitalia and skin.
- Cutaneous lesions are similar to those of erythema multiforme, although they are commonly haemorrhagic and are often vesicular or bullous.
- *Oral manifestations*
 - Lesions may be extremely severe and so painful that mastication is impossible.
 - Mucosal vesicles or bullae occur which rupture and leave surfaces covered with a thick white or yellow exudates.
 - Erosions of pharynx are also common.
 - Lips may exhibit ulceration with bloody crusting and are painful.
 - Oral lesions may be the chief complaint of the patient; it may be mistaken for ANUG.
 - Organisms of Vincent's infection are scarce in patients with this disease.
 - Mucosal involvement is more severe and extensive than erythema multiforme major.
- *Eye lesions*
 - It consists of photophobia, conjunctivitis, corneal ulceration and panophthalmitis.
 - Keratoconjunctivitis sicca is also reported.

- Blindness may result chiefly from recurrent bacterial infection.
- *Genital lesions:* Nonspecific urethritis, balanitis and/or vaginal ulcers.
- *Other complications*
 - Tracheobronchial ulceration
 - Pneumonia

Toxic epidermolysis necrolysis (lyell's disease)

- It is a very serious, often fatal, bullous drug eruption, so severe that large sheet of skin peel off, giving the appearance of a widespread scalding burn.
- Oral lesions may also occur.
- It should be differentiated from staphylococcal scalded skin syndrome, which appears clinically similar even though the latter is a milder disease with a better prognosis.
- It is often triggered by drug exposure.
- In contrast to erythema multiforme major, it occurs in older age group and shows female predilection.
- If the patient survives, then the cutaneous process resolves in 2–4 weeks. However, oral lesions may take longer time to heal and significant residual ocular damage is evident.

Histopathology

- It is not pathognomonic.
- Cutaneous or mucosal lesions generally exhibit intracellular oedema of the spinous layer of epithelium and oedema of the superficial connective tissue which may actually produce a subepidermal vesicle.
- Zone of severe liquefaction degeneration in the upper layers of the epithelium, intraepithelial vesicle formation and thinning with frequent absence of basement membrane.
- Dilatation of superficial capillaries and lymphatic vessels in the uppermost layer of connective tissue is prominent, and a varying degree of inflammatory cell infiltration, chiefly lymphocytes but often neutrophils and eosinophils, is also present.

Differential diagnosis

- Pemphigus
- Contact dermatitis or stomatitis

- ANUG

Prognosis and predictive factors

- Systemic corticosteroids are given especially in early stages of disease.
- Oral lesions can be managed effectively with topical corticosteroid syrups or elixirs.
- Causative drugs should be eliminated.
- IV rehydration is instituted for dehydrated patients.
- Topical anaesthesia will decrease discomfort for the patient.

Pemphigus

Definition

- Pemphigus is a group of potentially life-threatening autoimmune mucocutaneous disease characterized by epithelial blistering in cycles affecting cutaneous and/or mucosal surface.
- The word *pemphigus* is derived from Greek word *pemphix* meaning *bubble* or *blister.*
- It was named by Wichmann in 1971.

Types

1. Pemphigus vulgaris
2. Pemphigus foliaceus
3. Pemphigus vegetans
4. Paraneoplastic pemphigus
5. Familial benign pemphigus (Hailey–Hailey disease)

Commonly among all these variants, *pemphigus vulgaris and vegetans* have oral manifestations.

1. Pemphigus vulgaris (PV)

- *Vulgaris* is a Latin word, which means *common.*
- It is the most common type of pemphigus.
- It is an autoimmune, intraepithelial, blistering disease affecting the skin and mucous membrane and is mediated by circulating autoantibodies directed against keratinocytes cell surface.

Pathogenesis

- Blisters are associated with binding of IgG autoantibodies to keratinocyte cell surface molecules. These antibodies bind to keratinocyte desmosomes and desmosome-free areas of the keratinocyte cell membrane. The binding of autoantibodies results in a loss of cell-to-cell adhesion.
- Pemphigus antibody binds to keratinocyte cell surface molecules—desmoglein-1 and desmoglein-3.
- Desmoglein-3 is expressed in parabasal region of epidermis and oral epithelium.
- Desmoglein-1 is expressed in superficial portion of epidermis with minimal expression in oral epithelium.
- Patients with active disease have circulating and tissue-bound autoantibodies of both the immunoglobulin G*1* and G*4* subclasses.

Clinical features

- **Age.** 40–60 years.
- **Sex.** No sex predilection.
- **Location.** Palate, labial mucosa, buccal mucosa, ventral surface of the tongue and gingiva.
- **Signs and symptoms**
 - It is characterized by rapid appearance of vesicles and bullae varying from few millimetres to several centimetres.
 - It may contain a thin watery fluid shortly after development but may become purulent or sanguineous.
 - When vesicles rupture, they leave a raw eroded surface.
 - Loss of epithelium occasioned by rubbing apparently unaffected skin is termed *Nikolsky's sign.* It is a characteristic feature and is caused by perivesicular oedema which disrupts the epidermal–dermal junction.
 - *Oral manifestations*
 - Oral lesions precede skin lesions in majority of the cases.
 - Intact vesicles are rare in mouth, as soon as they form, they burst and form erosions.
 - Patients have ill-defined, irregularly shaped gingival, buccal or palatine erosions, which are painful and slow to heal.
 - Erosions can be seen on any part of the oral cavity and can be scattered and often extensive.
 - Erosions may spread and involve larynx with subsequent hoarseness.
 - Patient will be unable to eat or drink adequately.

- Other mucosal surfaces such as conjunctiva, oesophagus, labia, vagina, cervix, penis, urethra and anus may also be involved.

Histopathology (fig. 17.4)

- 'Intraepithelial vesicle' formation producing a distinctive suprabasilar split.
- Sometimes, entire superficial layers of the epithelium are stripped away leaving only the basal cells attached to the basement membrane and are described as resembling a 'row of tomb stones'.
- Prevesicular oedema appears to weaken this junction, and the intercellular bridges between epithelial cells disappear. This results in the loss of cohesiveness or 'acantholysis' because of which clumps of epithelial cells are often found lying free within the vesicular space. These cells are called *Tzanck cells.*
- Tzanck cell: It is characterized by degenerative changes which include swelling and hyperchromatic staining of round-shaped nuclei.
- Cytological diagnosis: *Tzanck test,* which demonstrates the presence of Tzanck cells in cytologic smears taken from early, freshly opened vesicles.
- Fluid in most of the vesicles, particularly more than 1 or 2 days old, contains variable numbers of polymorphonuclear leukocytes and lymphocytes.
- The relative scarcity of inflammatory cell infiltration, however, in both the vesicle and the bulla is suggestive of pemphigus, since other bullous diseases manifest marked inflammation.
- Immunofluorescence: IgG, IgM and C3 are demonstrated in the intercellular spaces between epithelial cells giving a typical 'fishnet pattern'.

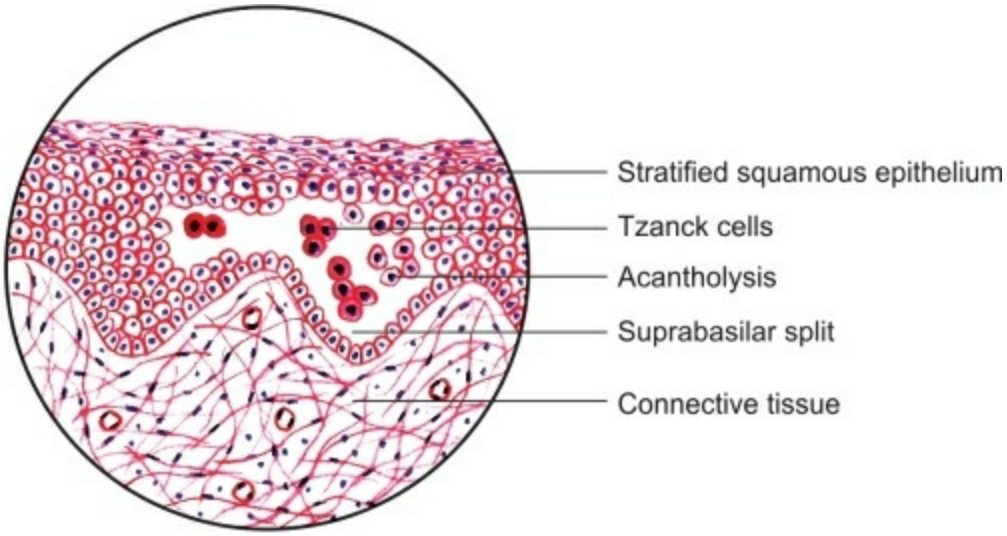


FIG. 17.4 Pemphigus vulgaris.

2. Pemphigus vegetans

- It is an uncommon variant of pemphigus vulgaris.
- It occurs in 1–2% of pemphigus vulgaris cases.
- Mean age of occurrence is 40–50 years.
- They may develop initially as flaccid bullae and erosions *(Neumann)* or pustules *(Hallopeau).*
- Both these subtypes develop in hyperpigmented vegetative plaques with pustules and hypertrophic granulation tissue at periphery.
- Lesions are located at intertriginous areas (where two skin areas may touch or rub together) and oral mucosa.
- Cerebriform tongue is characterized by pattern of sulci and gyri on the dorsum of the tongue.

3. Pemphigus foliaceus (PF)

(Synonyms: Superficial pemphigus; fogo selvagem)

- It is a benign variety of pemphigus.
- It is an autoimmune skin disorder characterized by the loss of intercellular adhesion of keratinocytes in the upper parts of epidermis (acantholysis) resulting in formation of superficial blisters.
- Clinical involvement of healthy appearing skin that blisters when rubbed (Nikolsky's sign).
- It is characterized by a chronic course, with little or no involvement of the mucous membranes.

Pathogenesis

- It is induced by IgG mainly IgG*4* subclass autoantibodies directed against a cell adhesion molecule, desmoglein 1, expressed mainly in the granular cell layer of epidermis.
- Precipitating factors: Medications and UV light radiation. Both factors enhance autoantibody epidermal binding, preferentially neutrophils adhesion to UV irradiated epidermis which contribute to acantholysis in photo-induced pemphigus foliaceus.

Clinical features

- **Age.** 40–60 years.
- **Sex.** No sex predilection.
- **Signs and symptoms**
 - Most commonly occurs among older adults, but sometimes occurs in young children also.
 - Little or no involvement of mucous membrane.
 - Early bullous lesions which rapidly rupture and dry to leave masses of flakes or scales.
 - Nikolsky's sign is positive.
 - It is a mild form of pemphigus.
 - *Brazilian pemphigus (fogo selvage, Brazilian wild fire):* It is a mild endemic form of pemphigus foliaceus found in tropical regions, particularly in Brazil.

Histopathology

- Acantholysis of upper epidermis is commonly seen.
- It usually enlarges and detaches without bulla formation, although a bulla may form showing acantholysis at both roof and floor.
- Established lesions may show acanthosis and mild to moderate papillomatosis.
- Hyperkeratosis and parakeratosis may occur with dyskeratotic cells within the granular layer.
- A mild dermal lymphocytic infiltrate occurs. Often with presence of eosinophils.

4. Paraneoplastic pemphigus

(Synonyms: Neoplasia-induced pemphigus; paraneoplastic autoimmune multiorgan syndrome)

- It is a rare vesiculobullous disorder that affects patients who have a neoplasm, usually lymphoma or chronic lymphocytic leukaemia.
- Anhalt et al first described it in 1990.

Pathogenesis

- Abnormal levels of cytokine, interleukin-6 (IL-6) produced by host lymphocytes in response to the patient's tumour.
- IL-6 is responsible for stimulating the abnormal production of antibodies directed against antigens associated with desmosomal complex and basement membrane zone of epithelium.

Clinical features

- **Age.** 50–70 years.
- **Sex.** No sex predilection.
- **Signs and symptoms**
 - Patients typically have a history of a malignant lymphoreticular neoplasm or less commonly a benign lymphoproliferative disorder such as angiofollicular lymph node hyperplasia (Castleman's disease or thymoma).
 - Most commonly associated malignancy with this disease is *non-Hodgkin's lymphoma.*
 - Other associated malignancies include chronic lymphocytic leukaemia, giant cell lymphoma, Waldenstrom macroglobulinemia, poorly differentiated sarcoma, bronchogenic squamous cell carcinoma, follicular dendritic cell sarcoma.
 - *Oral manifestations*
 - Site: Buccal and lingual mucosa, gingiva, nose, pharynx, conjunctiva and tonsils.
 - It presents with oral erosions or ulcerations.
 - Patients present with painful oral erosions, often accompanied by a generalized cutaneous eruption.
 - Eruption can assume a wide range of morphologies, including morbilliform, urticarial, bullous, papulosquamous, and erythema multiforme-like lesions.
 - Patients complain of pruritus or pain.
 - Erosions with subsequent crusting on vermilion of the lips are typical and similar to that seen in Stevens–Johnson syndrome.
 - Nasal ulcers may cause epistaxis.

- Conjunctival mucosa: Cicatrizing (scarring) conjunctivitis develops.

Histopathology

- Subepithelial clefting and intraepithelial clefting are commonly seen.
- Oral and cutaneous lesions show variable epidermal necrosis, suprabasal acantholysis, dyskeratotic keratinocytes, vacuolar interface dermatitis and lymphocytic infiltration.
- Oral mucosal lesions show greatest acantholysis, while some skin lesions may not show any acantholysis at all.
- Distinctive feature is dyskeratosis. Dyskeratotic keratinocytes are found at all levels in the epidermis, especially within the zones of acantholysis and also in cutaneous adnexa.
- Immunofluorescence: Positive deposition of IgG and C3 in intercellular zone of epithelium and/or linear deposition of immunoreactant at the basement membrane zone.

5. Familial benign pemphigus

(Synonym: Hailey–Hailey disease)

- It was originally described by Hailey brothers in 1939.
- It is a chronic autosomal dominant disorder with incomplete penetrance.
- Approximately two-thirds of patients have a family history of this disorder.
- A history of multiple relapses and remissions are the characteristic features.

Pathogenesis

- It is hypothesized that it results from a genetic defect in a calcium pump protein.
- The mutation is in *ATP2C1*, a gene localized on chromosome 3 (this genetic defect is similar to Darier disease).
- The contributing factors include heat, friction and infection.

Clinical features

- **Age.** Adolescence or young adults.
- **Sex.** No sex predilection.
- **Location.** Flexor surfaces of axilla and groin, neck and genital areas.
- **Signs and symptoms**
 - Lesions develop as small groups of vesicles appearing on normal or

erythematous skin, which soon rupture to leave eroded, crusted areas. These lesions then appear to enlarge peripherally but heal in the centre.
- Nikolsky's sign is positive.
- Heat and sweating amplify the outbreak of lesions while spontaneous remissions may occur in cold weather.
- Tender and enlarged regional lymph nodes may also be present.
- Bacterial infection also appears to precipitate the appearance of the lesion and more recently infection by *Candida albicans* has been implicated.
- *Oral manifestations*
 - Rare.
 - Lesions develop as crops of vesicles which rapidly rupture leaving raw eroded areas.

Histopathology

- It shows more extensive acantholysis than in pemphigus vulgaris and there is less damage to acantholytic cells.
- The characteristic feature is occasional intercellular bridges persist so that adjacent epithelial cells still adhere to each other and are not entirely acantholytic. This appearance is known as *dilapidated brick wall effect.*
- Benign dyskeratotic cells similar to the *corps ronds* of Darier disease may be present.

Differential diagnosis

- Dermatitis herpetiformis
- Bullous lichen planus
- Pemphigoid

Prognosis and predictive factors

- Treating superinfection
- Warm compresses
- Topical antibiotic ointments
- Immunosuppressive agents

Bullous pemphigoid

It is a chronic, autoimmune, subepithelial, blistering skin disease that rarely involves mucous membranes.

Pathogenesis

- It is characterized by the presence of IgG autoantibodies specific for the hemidesmosomal bullous pemphigoid antigens BP230 (BPAg1) and BP180 (BPAg2).
- IgG autoantibodies bind to the skin basement membrane and activate complement and inflammatory mediators.
- Activation of complement system is thought to play a critical role in attracting inflammatory cells to the basement membrane.
- These inflammatory cells are in turn postulated to release proteases, which degrade hemidesmosomal portions and lead to blister formation.
- Eosinophils are characteristically present, although their presence is not an absolute diagnostic criterion.

Clinical features

- **Age.** >60 years.
- **Sex.** No sex predilection.
- **Location.** Limbs, abdomen and neck region.
- **Signs and symptoms**
 - Cutaneous lesions begin as a generalized nonspecific rash, commonly on limbs which appear urticarial or eczematous and may persist for several weeks to months before the appearance of vesiculobullous lesions.
 - Vesicles and bullae arise in these prodromal skin lesions as well as in normal skin.
 - These vesicles and bullae are relatively thick-walled and may remain intact for some days.
 - Rupture does not occur always, but when it occurs it leaves a raw, eroded area which heals rapidly.
 - *Oral manifestations*
 - It occurs less frequently.
 - It appears as vesicles and areas of erosion and ulceration.
 - Gingival involvement generally involves much of the gingival mucosa and is exceedingly painful.
 - Gingival tissues appear extremely erythematous and may desquamate as the result of even minor frictional trauma.
 - Vesicles and ultimate erosions not only develop in gingival tissues but also in buccal mucosa, palate, floor of the mouth and tongue.

Histopathology (fig. 17.5)

- Vesicles and bullae are subepithelial and nonspecific.
- No evidence of acantholysis of epithelial cells; in fact, epithelium appears normal.
- Vesicles contain fibrinous exudates admixed with acute and chronic inflammatory cells and the presence of eosinophils within the vesicle/bullae is characteristic.
- Basement membrane remains attached to connective tissue rather than to overlying separated epithelium.
- Basement membrane also shows thickening with interruption of continuity.
- Immunofluorescence: IgG shows positivity in basement membrane zone.

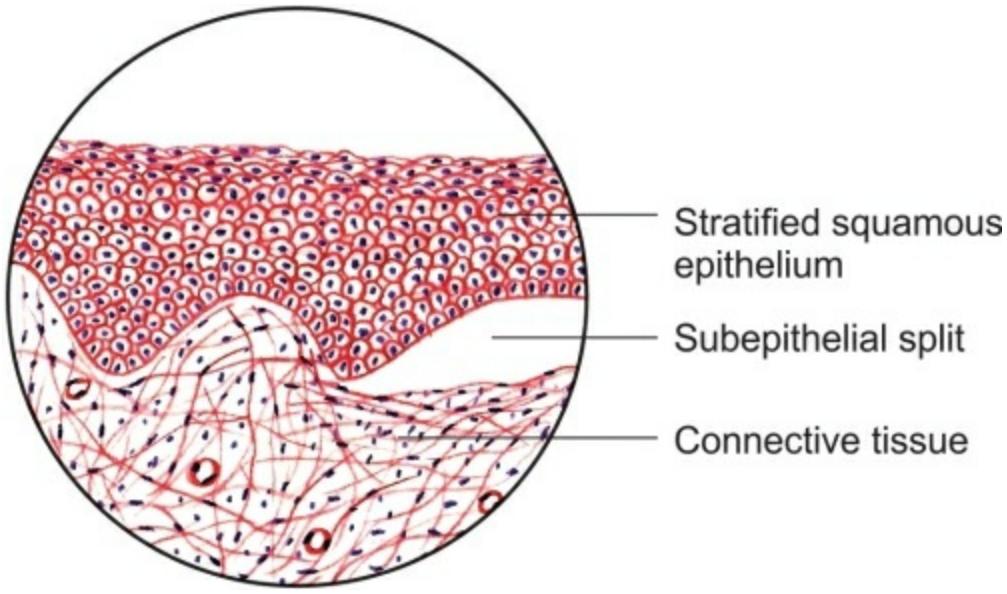


FIG. 17.5 Pemphigoid.

Prognosis and predictive factors

- Topical, intralesional or systemic corticosteroid therapy is indicated.
- Severe cases require immunosuppressive agents.

Cicatricial pemphigoid

(Synonyms: Benign mucous membrane pemphigoid; ocular pemphigus)

- It is an autoimmune blistering disease that predominantly affects the

mucous membrane including mouth, oropharynx, conjunctiva and genitalia.
- The sequelae of mucosal involvement result in decreased vision, blindness and supraglottic stenosis with hoarseness or airway obstruction.

Pathogenesis

- Autoantibodies are directed against basement membrane zone target antigens.
- Autoantibodies are IgG subclass IgG4. Sometimes, IgA antibodies are detected.
- Two major basement membrane antigens are *bullous pemphigoid antigen 2 (BPAG2* or *BP180)* and *epiligrin (laminin-5).*

Clinical features

- **Age.** 40–50 years.
- **Sex.** Female predilection.
- **Location.** Oral mucosa, conjunctiva, nose, pharynx, larynx, oesophagus, vagina, penis and anus.
- **Signs and symptoms**
 - Cutaneous involvement presents with tense blisters and erosions, often on head and neck or at sites of trauma.
 - These lesions heal by scar formation, particularly on conjunctiva.
 - Ocular involvement is the most serious complication of the disease.
 - Following initial conjunctivitis, adhesions develop between the palpebral and bulbar conjunctiva resulting in obliteration of palpebral fissure with opacity of cornea frequently leading to complete blindness.
 - *Oral manifestations*
 - Mucosal lesions are vesiculobullous in nature but appear to be relatively thick-walled and for this reason they may persist for 24–48 hours before rupturing and desquamating.
 - On rupturing, they leave a raw, eroded, bleeding surface.
 - Gingiva manifests as a persistent erythema for weeks or months after original erosions have healed.
 - Oral lesions rarely scar.
 - This disease is also termed as desquamative gingivitis.
 - *Ocular involvement*
 - One eye may be affected before the other.
 - The earliest change is subconjunctival fibrosis, which is usually

detected by an ophthalmologist using slit lamp examination.

- As the disease progresses, the conjunctiva becomes inflamed and eroded.
- Attempts at healing lead to scarring between the bulbar (lining the globe of eye) and palpebral (lining the inner surface of eyelid) conjunctivae and result in adhesion—*symblepharosis.*
- Scarring can ultimately cause the eyelids to turn inward—*entropion.*
- This causes eye lashes to rub against the cornea and globe—*trichiasis.*
- Scarring closes off the openings of lacrimal glands which lead to loss of tears and the eyes become extremely dry.
- The cornea then produces keratin as a protective mechanism; however, keratin is an opaque material and ensues blindness.
- End stage ocular involvement causes adhesion between the upper and lower eyelids.

Histopathology

- Vesicles and bullae are subepithelial in position.
- There is no evidence of acantholysis.
- Basement membrane structure appears to detach with the epithelium from the underlying connective tissue.
- There is a nonspecific chronic inflammatory infiltrate in the connective tissue, chiefly lymphocytes, plasma cells and eosinophils.
- Immunofluorescence: IgG, IgM, IgA and C3 show positivity in the basement membrane zone.

Differential diagnosis

- Pemphigus vulgaris
- Erosive lichen planus
- Bullous erythema multiforme

Prognosis and predictive factors

- Topical, intralesional or systemic corticosteroid therapy is indicated.
- Severe cases require immunosuppressive agents.

Epidermolysis bullosa

Epidermolysis bullosa (EB) is a group of inherited bullous disorders

characterized by blisters formation in the skin and mucosal membranes in response to mechanical trauma.

Classification

- EB simplex (EBS): Generalized form and localized form (Weber–Cockayne syndrome)
- EB dystrophic (DEB): It may be dominant or recessive
- Junctional EB (JEB)
- EB acquista (acquired)
- Hemidesmosomal EB (HEB)

Pathogenesis

- Defect in the attachment mechanisms of the epithelial cells either to each other or to the underlying connective tissue.
- Depending on the defective mechanism of cellular cohesion, it is categorized as follows:
 - EBS: Mutations in the genes encoding keratin 5 and 14.
 - JEB: Nonsense mutation in *LAMB3* gene encoding laminin-5
 - DEB: Mutations in the genes encoding type VII collagen (COL7A1). Anchoring fibrils are affected.
 - HEB: Mutation of genes associated with various hemidesmosomal attachment proteins—plectin, type XVII collagen (BP180) and α6B4 integrin.

1. Epidermolysis bullosa simplex

Clinical features

- Generalized form: Autosomal dominant, manifests at birth, vesicles and bullae on the hands and feet at sites of friction, blisters heal within 2–10 days with no scarring or permanent pigmentation.
- Localized form: Early in childhood or later in life, commonly recurrent, bullae develop on the hands and feet related to frictional trauma. No scarring upon healing.
- Oral manifestations: Very rare. Sometimes, bullae are seen. Teeth are not affected.

Histopathology

- Generalized form: Vesicles and bullae develop as a result of destruction of

basal and suprabasal cells, so that some nuclei persist on the floor of blister. Individual cells become oedematous and show dissolution of organelles and tonofibrils with displacement of nucleus to upper end of cells.

- Localized form: Bullae are intradermal and suprabasal in location (intraepithelial clefting).

2. Epidermolysis bullosa dystrophic: Dominant

Clinical features

- Onset in infancy or delayed until puberty.
- Blisters on the ankles, knees, elbows, feet and head.
- Healing results in scarring.
- Nails are thick and dystrophic.
- Milia (singular: milium) and small subepidermal keratocyst are seen.
- Palmar and plantar keratoderma, ichthyosis and hypertrichosis are seen.
- *Oral manifestations*
 - Typically mild with some gingival erythema and tenderness is seen.
 - Gingival recession and reduction in depth of buccal vestibule may be observed.
 - Oral milia is seen.
 - Teeth are unaffected.

Histopathology

- Subepithelial clefting (below the lamina densa) is seen.
- Basal layer appears normal although flattened on the roof of the blister.
- Connective tissue shows absence of elastic and oxytalan fibres.

3. Epidermolysis bullosa dystrophic: Recessive

Clinical features

- It is a classic form of the disease.
- Onset at birth or shortly thereafter.
- Sites: Feet, scapulae, elbows, fingers and occiput.
- Characterized by the formation of bullae spontaneously or at sites of trauma, friction or pressure.
- Bullae contain a clear, sterile or blood tinged fluid.
- Positive for Nikolsky's sign.

- Bullae heal by scar, milia and pigmentation.
- Hair may be sparse and nails are dystrophic or absent.
- *Oral manifestations*
 - Bullae, preceded by white spots or patches on oral mucosa or localized areas of inflammation.
 - Large areas of mucous membrane may be denuded.
 - Bullae are painful, scar formation results in obliteration of sulci and restriction of the tongue.
 - Repeated cycles of scarring result in scarring.
 - Bullae of larynx and pharynx: Hoarseness and dysphagia.
 - Dental defects: Rudimentary teeth, congenitally absent teeth, hypoplastic teeth and crowns denuded of enamel.

Histopathology

- Separation and bulla formation occur immediately beneath the poorly defined PAS-positive basement membrane which remains attached to the roof of the blister.
- Fragments of basement membrane may adhere to the dermis.
- Basal layer cells are normal.

4. Junctional epidermolysis bullosa

It is extremely fatal.

Clinical features

- Onset at birth.
- Absence of scarring, milia or pigmentation.
- Death may occur within 3 months of age. Death at birth results because of significant sloughing of skin during passage through birth canal.

Note: *Bullae* are similar to dystrophic recessive type except that they develop simultaneously and sheets of skin may shed.

- *Oral manifestations:* Oral bullae are very extensive and severe disturbances in enamel and dentine formation of deciduous teeth occur.

Histopathology.

Cleft at the level of lamina lucida of basement membrane is seen.

5. Epidermolysis bullosa acquisita

- No evidence of hereditary transmission.
- Similar to dystrophic form of the disease.
- Onset is in the adult life.

Differential diagnosis

- Pemphigus
- Erosive lichen planus
- Bullous erythema multiforme

Prognosis and predictive factors

- Topical, intralesional or systemic corticosteroid therapy is indicated.
- Severe cases require immunosuppressive agents.
- It cannot be cured, antibiotics can be given in case of secondary infections.

Lupus erythematosus

It is an immunologically mediated condition and is the most common collagen–vascular or connective tissue disease.

Clinicopathologic forms

- Systemic lupus erythematosus (SLE)
- Discoid lupus erythematosus (DLE) or chronic cutaneous lupus erythematosus (CCLE)
- Subacute cutaneous lupus erythematosus (SCLE)

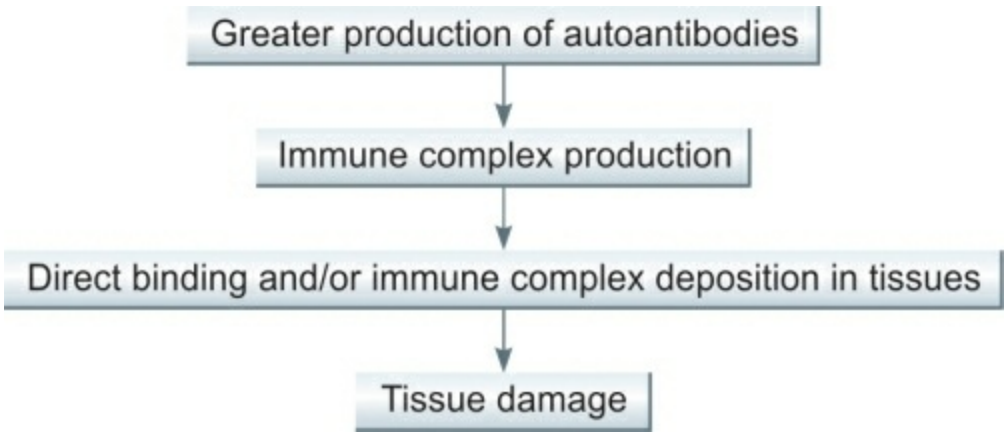
Systemic lupus erythematosus (SLE)

It is an autoimmune disease characterized by autoantibodies immune complex formation and immune dysregulation resulting in damage to any organ including kidney, skin, blood cells and CNS.

Pathogenesis

- Predisposing factors:
 - Genetic predisposition
 - Hormones and environment factors (e.g. sunlight, drugs)

 - Viral infection
 - Immunologic abnormality
- Antibodies may be produced in reaction to exposure of normally unexposed self-antigens.
- Immune dysregulation results in excessive production of many antibodies without regard to prior stimulation.
- SLE produces autoantibodies against DNA, other nuclear antigens, ribosomes, platelets, erythrocytes, leukocytes and other tissue-specific antigens.
- Pathogenesis of SLE is illustrated in Flowchart 17.2.



FLOWCHART 17.2 Pathogenesis of systemic lupus erythematosus

Clinical features

- **Age.** 30–40 years.
- **Sex.** Female predilection.
- **Location.** Neck, upper arms, shoulders, fingers, lower lip, buccal mucosa and tongue.
- **Signs and symptoms**
 - SLE is a prototypical example of an immunologically mediated inflammatory condition that causes multiorgan damage.
 - The oral lesions of systemic lupus are generally similar to those of discoid lupus and are most prevalent on the buccal mucosa, followed by the gingival tissues, the vermilion border of the lip, and the palate, in decreasing order of frequency.
 - The lesions are frequently symptomatic, especially if the patient ingests

hot or spicy foods, and often consist of one or more of the following components: erythema, surface ulceration, keratotic plaques and white striae or papules.

- Typical cutaneous lesions appear as red and somewhat scaly patches that favour sun-exposed areas and typically form a 'butterfly-shaped' rash (malar rash) over the cheeks and bridge of the nose. These lesions characteristically expand by peripheral extension and are usually disc-shaped.
- The oral lesions can occur in the absence of skin lesions, but there is a strong association between these two. As the lesions expand peripherally, there is central atrophy, scar formation and occasional loss of surface pigmentation. Lesions often heal in one area only to occur in a different area later.
- The lesions may be atrophic, erythematous and/or ulcerated, and are often painful.
- *Systemic involvement*
 - Kidney: Fibrinoid thickening of glomerular capillaries produces characteristic wire loops—renal insufficiency—renal failure.
 - Heart: Atypical endocarditis involving valves as well as fibrinoid degeneration of epicardium and myocardium is seen. At autopsy nearly 50% of SLE patients display warty vegetations affecting the heart valves—*Libman–Sacks endocarditis.*

Discoid lupus erythematosus (DLE) or chronic cutaneous lupus erythematosus (CCLE)

- It is a chronic, scarring, atrophy producing, photosensitive dermatosis.
- DLE can occur in patient with SLE.
- DLE can progress to SLE.

Pathogenesis

- DLE probably occurs in genetically predisposed individuals but exact genetic connection has not been determined.
- Heat shock protein is induced in keratinocytes following UV light exposure or stress. This protein acts as a target for T cell-mediated epidermal cell cytotoxicity.

Clinical features

- **Age.** 30–40 years.
- **Sex.** Female predilection.
- **Location.** Face, oral mucosa, chest, back and extremities.
- **Signs and symptoms**
 - *Cutaneous lesions*
 - Slightly elevated red or purple macules often covered by grey or yellow adherent scales.
 - Forceful removal of scales reveals numerous 'carpet tack' extensions which had dipped into enlarged pilosebaceous canals.
 - These lesions increase in size by peripheral growth.
 - Periphery of lesion appears pink or red, while the centre exhibits an atrophy with scarring and hypopigmentation or hyperpigmentation indicative of long-standing nature of disease with characteristic central healing.
 - Butterfly distribution on malar region and across the bridge of nose can also be seen.
 - Conjunctival involvement by DLE has rarely been reported to cause cicatrizing conjunctivitis.
 - Occasionally, epidermoid carcinoma and less commonly basal cell carcinoma develop in scars of DLE.
 - *Oral manifestations*
 - Oral lesions involve either prior to or following the development of skin lesions or even absence of skin manifestations.
 - Lesions begin as erythematous areas, sometimes slightly elevated but more often depressed, usually without induration.
 - An ulcerated or atrophic, erythematous central zone, surrounded by white, fine, radiating striae is seen.
 - Sometimes, the erythematous, atrophic central region of a lesion may show fine stippling of white dots.
 - Central healing may result in depressed scarring.
 - Most commonly vermilion border of lower lip is involved. The erythematous atrophic plaques surrounded by keratotic border are seen. They may involve the entire lip and extend on to the skin surface. Malignant transformation of these lip lesions can occur sometimes.

Subacute cutaneous lupus erythematosus (SCLE)

- Patients with SCLE have clinical manifestations intermediate between

those of SLE and CCLE.

- The skin lesions are the most prominent feature of this variation.
- These are characterized by photosensitivity and are therefore generally present in sun-exposed areas.
- These lesions do not show induration and scarring.
- Usually, renal or neurologic abnormalities are not present, but sometimes arthritis or musculoskeletal problems are seen.

Histopathology

- SLE and DLE are similar, differing only in the degree of certain findings.
- According to Lever, DLE of skin is characterized by:
 - Hyperorthokeratosis with keratotic plugs.
 - Atrophy of the rete ridges.
 - Liquefactive degeneration of the basal cell layer.
 - Perivascular infiltration of lymphocytes and their collection about dermal appendages.
 - Basophilic degeneration of collagen and elastic fibres with hyalinization, oedema and fibrinoid change, particularly prominent immediately beneath the epithelium.
- Not all features are invariably present in each case.
- However, in SLE, cutaneous lesions are similar in appearance although, the degenerative features and collagen disturbances are usually more prominent and the inflammatory features are less severe.
- According to Shkler and McCarthy, oral lesions of DLE show:
 - Hyperkeratosis with areas of epithelial atrophy.
 - Keratotic plugging down into the spinous layer, acanthosis and pseudoepitheliomatous hyperplasia are present.
 - Hydropic degeneration and liquefaction necrosis of basal cell layer are seen.
 - Subepithelial vesiculation or ulceration is present.
 - Thickening of basement membrane can be demonstrated as a homogenous, broad, eosinophilic and PAS-positive acellular band.
 - Diffuse infiltrate of lymphocytes with smaller number of plasma cells and occasional polymorphonuclear leukocytes in superficial and deep connective tissue.
 - Small focal perivascular collection of lymphocytes is found.
 - Degeneration and disintegration of collagen is seen.
- SLE shows identical histologic features in oral lesions to those in the DLE

with the possible exception of the absence keratinization:

- Another important finding in lupus is that direct immunofluorescence testing of lesional tissue shows the deposition of various immunoglobulins and C3 in a granular band involving the basement membrane zone.
- Importantly, direct immunofluorescent testing of uninvolved skin in a case of SLE will show a similar deposition of immunoglobulins and/or complement. This is called the *positive lupus band test,* and discoid lesions will not show this result.

Laboratory findings

- The lupus erythematosus (LE) cell test consists of incubating the patient's serum with normal white blood cells (WBCs). In the presence of antibody to whole nucleoprotein (LE factor), damage to nuclei of leukocytes incite phagocytosis of affected nuclei by unaffected WBCs. If a smear of incubated WBCs is made and stained with Wright's stain, the phagocytized nuclear material may be observed within some of the neutrophils as a large, round, amorphous, smoky, basophilic body of such a large size that it presses the nucleus of neutrophil against the cell membrane. This represents the LE cell.
- Rarely, LE cells are found in DLE.

Differential diagnosis

- Pemphigus
- Lichen planus
- Contact dermatitis or stomatitis

Prognosis and predictive factors

Steroids therapy can be given.

Systemic sclerosis

(Synonyms: Scleroderma; dermatosclerosis; Hide-Bound disease)

Systemic sclerosis (SS) is a systemic connective tissue disease characterized by vasomotor disturbances, fibrosis, subsequent atrophy of the skin, subcutaneous tissues, muscles and internal organs (e.g. GIT, lungs, heart, kidney, CNS) with associated immunologic disturbances.

Pathogenesis

- Autoimmune disease: The overproduction of collagen is thought to result from an autoimmune dysfunction.
- Genetic, environmental, vascular factors are thought to be causative factors to stimulate the fibroblasts.
- Antigens from the human leukocyte antigen (HLA) histocompatibility complex including HLA-B8, HLA-DR5, HLA-DR3, HLA-DR52 and HLA-DQB2 are involved.

Clinical features

- **Age.** 30–40 years.
- **Sex.** Female predilection.
- **Location.** Usually begins on face, hands or trunk.
- **Signs and symptoms**
 - It is characterized by ultimate fixation of the epidermis to the deeper subcutaneous tissues.
 - Skin appears yellow, grey or ivory white waxy.
 - Skin becomes hardened and atrophic and cannot be wrinkled (firm fixation to the deep connective tissue)—*mask-like face and claw-like fingers to the hands.*
 - Systemic sclerosis ultimately involves many internal organs like GIT, lungs, CVS, CNS and renal system.
 - Circumscribed scleroderma (morphea): Well-defined, slightly elevated or depressed cutaneous patches, white or yellowish and surrounded by violaceous halo.
 - Localized scleroderma: It affects only a solitary patch of skin. Occasionally, lesions occur as linear bands or ribbon on the face, particularly the forehead, of the chest and trunk or on an extremity —*linear scleroderma.* Such band is made up of furrow with an elevated ridge on one side—*Coup de Sabre,* since it resembles the mark produced by blow of saber.
 - A variant of systemic scleroderma is *CREST syndrome (C—calcinosis cutis, R—Raynaud's phenomenon, E—oesophageal dysfunction, S—sclerodactyly, T—telangiectasia).*
 - *Oral manifestations*
 - Site: Tongue, soft palate and larynx.
 - Early features include mild oedema followed by atrophy and induration of mucosal and muscular structures.

- Tongue—stiff and board-like causing difficulty in eating and speaking.
- Gingival tissue—pale and firm.
- Lips—thin, rigid and partially fixed.
- Dysphagia
- Inability to open and close the mouth.
- Limitation of mouth opening.
- Widening of the periodontal ligament (2–4 times the normal thickness).
- Bilateral bone resorption of the angle of the mandibular ramus.
- Partial or complete resorption of condyles and coronoid processes of mandible.

Radiographic features

- Diffuse widening of periodontal ligament space throughout the dentition.
- Varying degrees of resorption of posterior ramus of the mandible, coronoid process, chin and condyle may be detected, usually bilaterally. Theoretically, these areas are resorbed because of increased pressure associated with the abnormal collagen production.
- Individual tooth resorption has also been reported.

Histopathology

- Thickening and hyalinization of collagen fibres in the skin.
- Loss of dermal appendages.
- Atrophy of the epithelium with loss of rete pegs.
- Increased melanin pigmentation.
- Increased PAS-positive, diastase-resistant material present in the areas of the homogenous material.
- Widening of periodontal ligament is due to increase of collagen and oxytalan fibres, hyalinization and sclerosis of collagen with decrease in number of connective tissue cells.

Prognosis and predictive factors

- There is no cure for scleroderma, only symptomatic treatment is available.
- Cortisone therapy can be given.

Key points

- *Genodermatoses* are hereditary skin disorders with oral manifestations caused due to genetic defects.
- *Ectodermal dysplasias* are a heterogenous group of disorders characterized by congenital dysplasia of two or more ectodermal structures and their appendages.
- *Ehlers–Danlos syndrome:* Joint hypermobility, hyperelasticity of skin, dystrophic scars, excessive bleeding, ecchymoses and haematomas.
- *White sponge naevus:* Defect in normal keratinization process of oral mucous membrane.
- *Pachyonychia congenita:* Dystrophic nails, focal palmoplantar keratoderma and oral leukokeratosis.
- *Dyskeratosis congenital:* Reticular hyperpigmentation of skin, dystrophic nails, mucous membrane leukoplakia and pancytopenia. It has increased prevalence of malignant neoplasm.
- *Oral lichen planus* variants: Reticular, papillary, atrophic, erosive, bullous and plaque-like lesions.
- *Oral lichen planus* shows hyperkeratosis, saw-tooth shaped rete pegs, liquefaction, degeneration of basal cell layer, Civatte bodies and dense subepithelial band of lymphocytes.
- *Erythema multiforme* is an acute, hypersensitive, self-limiting and sometimes recurring condition associated with certain infections, medications and various triggers factors.
- *Pemphigus* is a group of potentially life-threatening autoimmune mucocutaneous disease characterized by epithelial blistering in cycles affecting cutaneous and/or mucosal surface.
- *Pemphigus variants:* Pemphigus vulgaris, pemphigus foliaceus, pemphigus vegetans, paraneoplastic pemphigus and familial benign pemphigus.
- *Tzanck cells* are degenerative cells which shows swelling and hyperchromatic, round-shaped nuclei and commonly seen in pemphigus and herpes simplex virus.
- *Cicatricial pemphigoid* is an autoimmune subepithelial blistering disease that predominantly affects mucous membrane and these lesions heal by scar formation.
- *Epidermolysis bullosa* is a group of inherited bullous disorders characterized by blisters formation in the skin and mucosal membranes in response to mechanical trauma.
- *Systemic lupus erythematosus* is an autoimmune disease characterized by autoantibodies immune complex formation and immune dysregulation

resulting in the damage to any organ.

- *Discoid lupus erythematosus* is a chronic, scarring, atrophic and photosensitive dermatosis.
- *CREST syndrome:* C—Calcinosis cutis, R—Raynaud's phenomenon, E—Oesophageal dysfunction, S—Sclerodactyly, T—Telangiectasia.

Frequently asked questions

1. Genodermatoses.
2. Ectodermal dysplasia.
3. Ehlers–Danlos syndrome.
4. Goltz–Gorlin syndrome.
5. White sponge naevus or Cannon's disease.
6. Darier disease.
7. Direct immunofluorescence/indirect immunofluorescence.
8. Write about pathogenesis, clinical features and histopathology of lichen planus/Civatte bodies
9. Histopathology of psoriasis.
10. Discuss pathogenesis, clinical features and histopathology of erythema multiforme or Stevens–Johnson syndrome or target lesions.
11. Write about pathogenesis, clinical features and histopathology of pemphigus or Nikolsky's sign or Tzanck cells.
12. Pemphigoid or pemphigus versus pemphigoid.
13. Epidermolysis bullosa.
14. Lupus erythematosus.
15. Systemic sclerosis.

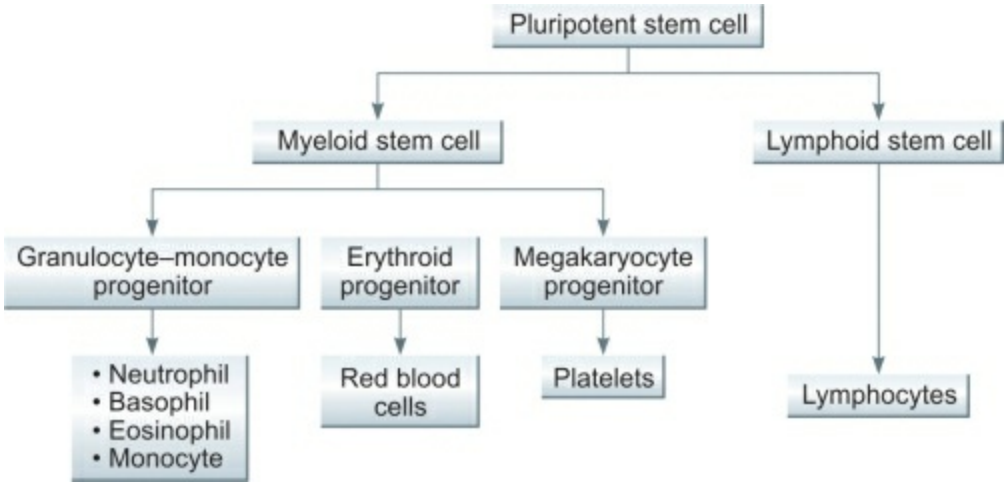
CHAPTER 18

Diseases of the blood and blood forming organs

Haematopoiesis (haemato—blood, poiesis—production)

Haematopoiesis is a process of blood cell formation. In the human embryo, the *yolk sac* is the main site of haematopoiesis in the first few weeks of gestation. By 3rd month, the *liver* and *spleen* become the main sites of blood cell formation and continue to do so until about 2 weeks after birth. Haematopoiesis commences in the *bone marrow* by 4–5 months in utero and becomes fully active by 7th and 8th month so that at birth practically all bones contain active marrow. During normal childhood and adult life, therefore, the marrow is the only source of new blood cells. However, during childhood, there is progressive fatty replacement throughout the long bones so that by adult life the haematopoietic marrow is confined to the central skeleton (vertebrae, sternum, ribs, skull, sacrum and pelvis) and proximal ends of femur, tibia and humerus.

- Haematopoiesis is illustrated in Flowchart 18.1.
- Blood cells include red blood cells, neutrophils, basophils, eosinophils monocyte, platelets and lymphocytes (Fig. 18.1).



FLOWCHART 18.1 Haematopoiesis

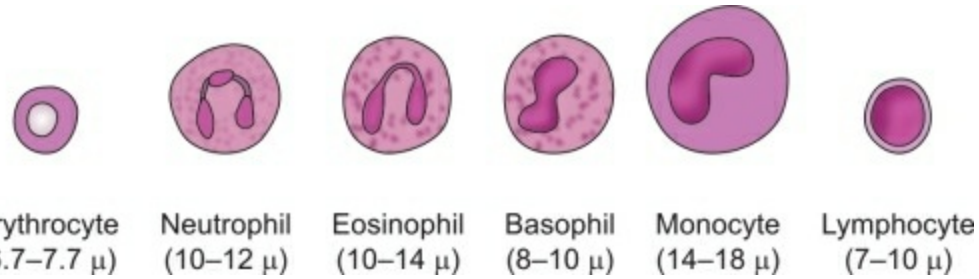


FIG. 18.1 Blood cells.

Erythropoiesis (erythro—red, poiesis—production)

The formation of red blood cells is known as erythropoiesis. The erythroid series of cells are as follows:

- **Pronormoblast or proerythroblast:** It is a large cell, 15–20 μm in diameter having deeply basophilic cytoplasm and large central nucleus containing nucleoli. The basophilic cytoplasm is due to high content of RNA which is associated with active protein synthesis.
- **Early normoblast:** It is a round cell having a diameter of 12–16 μm with a large nucleus which is slightly more condensed than the pronormoblast and contains basophilic cytoplasm.
- **Intermediate normoblast:** The cell has a diameter of 12–14 μm. The nucleus will be coarse and deeply basophilic. The cytoplasm is characteristically polychromatic, i.e. contains admixture of basophilic RNA and acidophilic haemoglobin.
- **Late normoblast:** It is a final stage in the maturation of nucleated red cells. The cell at this stage is smaller, 8–12 μm in diameter, containing a small and pyknotic nucleus with dark nuclear chromatin. The cytoplasm is characteristically acidophilic with diffuse basophilic hue due to the presence of large amounts of haemoglobin.
- **Reticulocytes:** These cells are juvenile red cells devoid of nucleus but contain ribosomal RNA so that they are still able to synthesize haemoglobin. Reticulocytes spend 1–2 days in the marrow and circulate for 1–2 days in the peripheral blood before maturing in the spleen, to become a biconcave red cell.

Anaemiae

- Anaemia is defined as an abnormal reduction in number of circulating red blood cells, the quantity of haemoglobin and the volume of packed red cells in a given unit of blood per age, sex and attitude of the individual.
- The two widely accepted classifications of anaemiae are based on pathophysiology and morphology of red blood cells.

Pathophysiologic classification

Depending upon the pathophysiologic mechanism, anaemiae are classified

as follows:

- *Anaemia due to increased blood loss*
 - Acute blood loss anaemia
 - Chronic blood loss anaemia
- *Anaemia due to impaired red cell production*
 - Cytoplasmic maturation defects:
 - Deficient haeme synthesis—iron-deficiency anaemia
 - Deficient globin synthesis—thalassaemic anaemias
 - Nuclear maturation defects: Vitamin B_{12} and/or folic acid deficiency—megaloblastic anaemia
 - Defect in stem cell proliferation and differentiation:
 - Aplastic anaemia
 - Pure red cell aplasia
 - Anaemia of chronic disorders
 - Bone marrow infiltration
 - Congenital anaemia
- *Anaemiae due to increased red cell destruction (haemolytic anaemia)*
 - Extrinsic (extracorpuscular) red cell abnormalities
 - Intrinsic (intracorpuscular) red cell abnormalities

Morphologic classification

Based on the red cell size, haemoglobin content and red cell indices, anaemiae are classified as follows:

- *Microcytic, hypochromic:* Mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) are all reduced, e.g. iron–deficiency anaemia, sideroblastic anaemia, thalassaemia, anaemia due to chronic disorders.
- *Normocytic, normochromic:* MCV, MCH and MCHC are all normal, e.g. anaemia due to acute blood loss, haemolytic anaemia and bone marrow failure.
- *Macrocytic, normocytic:* MCV, MCH and MCHC are all raised, e.g. megaloblastic anaemia.

Iron-deficiency anaemia

- Iron-deficiency anaemia is the most common of all anaemiae, affecting approximately 30% of the world's population.
- It is a hypochromic microcytic anaemia.

Pathogenesis

- *Chronic blood loss:* Menstrual or menopausal bleeding, parturition, bleeding haemorrhoids, or a bleeding malignant lesion or ulcer in the gastrointestinal tract.
- *Decreased rate of absorption of iron:* Malabsorption syndromes, subtotal or complete gastrectomy, habit of clay eating.
- *Inadequate dietary intake of iron:* Poor economic status, anorexia and elderly individuals.
- *Increased requirements:* Spurts of growth in infancy, childhood and adolescence, prematurity, and pregnancy and lactation.

Clinical features

- **Age.** 20– 45 years.
- **Sex.** Female predilection.
- **Signs and symptoms**
 - Fatigue, anorexia, headache, lassitude, tachycardia.
 - Pallor of skin, mucosa and koilonychias (spoon-shaped nails).
 - Tendency of the nails to crack and split.
 - Atrophy of oral and oesophageal mucous membrane is seen.
 - The tongue may become smooth due to atrophy of the filiform and fungiform papillae, and glossodynia (painful tongue) can be a presenting or an associated symptom.
 - In long-standing cases, oesophageal strictures or webs can develop, resulting in dysphagia.
 - Delayed wound healing after surgical procedures.
 - Angular cheilitis and oral candidiasis are common findings.
 - Buccal scrapings reveal decreased keratinization of cells, reduced cytoplasmic diameter, enlarged nucleus with nucleoli and karyorrhexis (fragmentation of nucleus).

Laboratory findings

- Hypochromic microcytic anaemia.
- RBC count is reduced.
- Hb% is decreased.
- Serum iron concentration is decreased.

Prognosis and predictive factors

- Iron supplements are instituted.
- The most important aspect of treatment is identification of the cause, especially a source of occult blood loss.
- ***Dental considerations***
 - Elective oral surgical or periodontal procedures should not be performed on patients with marked anaemia because of the potential for increased bleeding and impaired wound healing.
 - When haemoglobin levels fall below 10 g/dl, the low oxygen tension affects the interactions between the cellular components of blood, mainly platelets and endothelium, decreasing their ability to clot effectively.
 - General anaesthesia should not be administered unless the haemoglobin is at least 10 g/dl.

Plummer–Vinson syndrome

(Synonyms: Paterson–Kelly syndrome; Sideropenic dysphagia)

- It was first described by Plummer and Vinson.
- It is characterized by dysphagia, iron-deficiency anaemia and oral lesions.
- It commonly affects middle-aged women.
- A smooth and sore tongue, dry mouth, spoon-shaped nails and angular stomatitis are common findings.
- Atrophy of the tongue papillae is seen, but it is less severe than in pernicious anaemia.
- Atrophic changes are seen in the oral mucosa, the pharynx, the upper oesophagus and the vulva.
- Tissues are dry, inelastic and glazed in appearance.
- Listlessness, pallor, ankle oedema and dyspnoea are seen.
- The dysphagia, which represents an important feature of this condition, appears to be the result of muscular degeneration in the oesophagus and strictures or webs of the oesophageal mucosa.
- The oesophageal lesions (post-cricoid web) are demonstrable radiographically (barium swallow) or by oesophagoscopy. Because many of the symptoms in this syndrome are similar to those observed in vitamin B complex deficiency and simple hypochromic anaemiae, treatment includes B complex and iron supplements.
- Plummer–Vinson syndrome is potentially serious because of increased predisposition to leukoplakia and squamous cell carcinoma.
- Patients should be followed up at short intervals and checked for the

development of lesions that raise the suspicion of malignancy.

Pernicious anaemia

(Synonyms: Primary anaemia; Addison's anaemia; Biermer's anaemia)
Pernicious anaemia is a megaloblastic anaemia that occurs due to vitamin B_{12} (cobalamin) deficiency.

Pathogenesis

- *Impaired absorption of vitamin B_{12}* due to atrophy of the gastric mucosa resulting in a lack of intrinsic factor secretion. Intrinsic factor is a protein secreted by parietal cells and it promotes absorption of vitamin B_{12} molecule.
- *Autoimmune reaction* to either the gastric parietal cells or intrinsic factor.
- *Dietary deficiency:* Strict vegetarians over a period of time tend to suffer from vitamin B_{12} deficiency as it is available only in eggs, meat and milk.
- *Malabsorption:* Secondary to inadequate gastric production or defective functioning of intrinsic factor.
- *Other causes of deficiency:* Gastrectomy, diverticulitis, coeliac disease, Crohn's disease, alcoholism and prolonged use of drugs like neomycin, colchicine and proton pump inhibitors.

Clinical features

- **Age.** >30 years.
- **Sex.** No sex predilection.
- **Signs and symptoms**
 - *Symptoms triad:* Weakness, sore or painful tongue, numbness of extremities.
 - Weakness, fatigue, shortness of breath and neurologic abnormalities like incoordination, loss of vibratory sensation, drowsiness, etc.
 - *Oral manifestations*
 - Glossitis and glossodynia are the classic oral symptoms.
 - The tongue is *beefy red* and inflamed, with small erythematous areas on the tip and margins. There is a loss of filiform papillae, and, in advanced disease, the papillary atrophy involves the entire tongue surface together with a loss of the normal muscle tone.
 - Diffuse erythematous macular lesions are seen in buccal and labial

mucosa.
- Dysphagia and altered taste sensation.
- Discomfort described by denture wearers who have pernicious anaemia is probably due to the weakened mucosal tissues.
- The glossitis in pernicious anaemia is also known as *Hunter's glossitis.*
- Nonspecific aphthous like ulcerations.
- The *burning mouth* sensation is present, which may be due to a neuropathy.

Laboratory findings

- Macrocytosis is common.
- MCV, MCH and MCH concentration will be normal.
- Howell–Jolly bodies are seen.
- Hypersegmented neutrophils.
- Buccal scrapings reveal nuclear abnormalities.
- Schilling test reveals vitamin B_{12} deficiency.

Prognosis and predictive factors

- Administration of parenteral cyanocobalamin.
- Large oral doses may be used when intramuscular injection is contraindicated.

Aplastic anaemia

- Aplastic anaemia (AA) is a rare, life-threatening, haematologic disorder characterized by failure of the haematopoietic precursor cells in bone marrow to produce adequate number of all types of blood cells.
- Aplastic anaemia is defined as pancytopenia (simultaneous presence of anaemia, leucopenia and thrombocytopenia) resulting from aplasia of the bone marrow.
- The term *anaemia* is a misnomer, since all three cellular elements of the marrow are often involved (pancytopenia).

Types

- *Primary AA*
 - Fanconi anaemia (bone abnormalities, microcephaly, hypogenitalism, olive brown skin pigmentation): Congenital

- Immunologically mediated anaemia: Acquired
- *Secondary AA:* Drugs, toxic chemicals, infections and radiation (acquired form)

Clinical features

- **Age.** Any age group.
- **Sex.** Female predilection.
- **Signs and symptoms**
 - It includes signs and symptoms of anaemia.
 - Patients are more susceptible to infection.
 - Easy bruising and bleeding, retinal and cerebral haemorrhages are seen.
 - *Oral manifestations:* Gingival bleeding, petechiae, purpura, ecchymoses and gingival hyperplasia are seen.

Prognosis and predictive factors

- Spontaneous recovery is seen in milder forms.
- Withdrawal of offending agent is necessary.
- Supportive care: Antibiotics, blood transfusions, control of bleeding, etc.
- Bone marrow transplant or stem cell transplant (<40 years).
- Prognosis depends on severity.

Haemolytic anaemia

The haemolytic anaemias are a group of anaemiae which result from decreased survival of erythrocytes, either intermittently or continuously, resulting from intracorpuscular defects in the erythrocytes (often hereditary) or from extracorpuscular factors.

Pathogenesis

- **Extracorpuscular factors**
 - Overwhelming infections and toxins
 - Cardiac valvular prostheses
 - Rh factor incompatibility (haemolytic disease of newborn, erythroblastosis fetalis)
 - Chronic liver disease
 - Autoimmune haemolytic disease
 - Transfusion reactions

- **Intracorpuscular defects**
 - Abnormal shape of the erythrocytes:
 - Hereditary spherocytosis
 - Hereditary elliptocytosis
 - Paroxysmal nocturnal haemoglobinuria
 - Erythrocyte enzyme deficiencies:
 - Glucose-6-phosphate dehydrogenase deficiency
 - Pyruvate kinase deficiency
- **Abnormal haemoglobins (haemoglobinopathies)**
 - Sickle cell anaemia and sickle cell trait
 - Thalassaemia
- **Other haemoglobinopathies** (e.g. haemoglobin C and F)

Clinical features

- **Age.** Any age group.
- **Sex.** Female predilection.
- **Signs and symptoms**
 - Pallor of nail beds and palpebral conjunctiva are seen.
 - Pallor of the oral mucosa includes soft palate, tongue and floor of the mouth.
 - Jaundice: Icterus of sclera, but the skin, soft palate and tissues of the floor of the mouth.
 - Splenomegaly.

Radiographic features

- Hyperplastic bone marrow.
- Increased bone radiolucency with prominent lamellar striations.

Laboratory findings

- Mild to moderate anaemia
- Reticulocytosis
- Prominent spherocytosis in peripheral blood smear
- Positive Coombs' (antiglobulin) test for the presence of warm antibodies on the red cells at 37°C

Prognosis and predictive factors

- Supportive care: Antibiotics for infections

- Blood transfusions

Sickle cell anaemia

- Sickle cell disease is an autosomal recessive disorder characterized by an abnormality in the β-chain of haemoglobin.
- The lowered blood oxygen tension or an increased blood pH causes sickle-shaped crystal (a tactoid) of haemoglobin within the erythrocyte.
- This sickling of the erythrocyte leads to stasis and haemolysis of the red cells, especially in end-capillary circulation. The stasis then results in an even lower oxygen tension, an increased pH and further sickling.

Pathogenesis

- A normal haemoglobin (Hb) molecule consists of two pairs of amino acid chains, the α- and β-chains and is represented as *HbA*. Fetal Hb *(HbF)*, normal in fetal life, is considered abnormal, if persisted in adult life, which has two γ-chains in place of two β-chains.
- Sickle cell disease involves a single amino acid abnormality: The glutamic acid normally found in position 6 of the β-chain is replaced by valine. This Hb is represented as *HbS*.
- Patients with sickle cell trait are not anaemic and have no symptoms of their disease unless they are placed in situations where there is abnormally low oxygen, such as in an unpressurized airplane or under injudicious administration of general anaesthesia. On the other hand, patients with sickle cell anaemia usually exhibit marked clinical manifestations.

Clinical features

- **Age.** <30 years.
- **Sex.** Female predilection.
- **Signs and symptoms**
 - Patients show marked underdevelopment and often die before 40 years of age.
 - The clinical manifestations are the results of the basic anaemia and haemolytic process (jaundice, pallor and cardiac failure) or of necrosis following stasis of blood and vaso-occlusion.
 - *Susceptibility to infections* of *S. pneumoniae*.
 - *Sickle cell crisis:* Severe sickling due to hypoxia, infection, hypothermia,

dehydration lasting for 3 to 10 days. In these crises, the patient becomes acutely ill, red cell production virtually stops and the haemoglobin drops precipitously.
- Patients often show delayed eruption and hypoplasia of the dentition secondary to their general underdevelopment.
- Patients are more prone to develop osteomyelitis.

Radiographic features

- Increased erythropoietic activity and marrow hyperplasia attempt to compensate for the haemolysis and manifest as increased radiolucency. This change is noted especially in the alveolar bone between the roots of the teeth, where the trabeculae may appear as horizontal rows, creating a *ladder-like effect*.
- In lateral skull radiographs, the diploe is thickened, and the trabeculae are coarse and tend to run perpendicular to the inner and outer tables, which gives a *hair-on-end* appearance.
- Generalized osteoporosis.

Laboratory findings

- Haemoglobin is reduced.
- Sickle-shaped RBCs are seen in peripheral blood smear.

Prognosis and predictive factors

- Only supportive care is possible.
- Prophylactic penicillin therapy for infants diagnosed with sickle cell disease up to 5 years.
- Pneumococcal vaccinations.
- Transfusions are avoided unless the patient has an aplastic crisis with a resulting extremely low haemoglobin level.
- Increased risk of complications secondary to chronic anaemia and delayed wound healing.
- General anaesthesia should be used with caution in patients with sickle cell trait or sickle cell anaemia; when used, it is imperative to avoid episodes of hypoxia because cerebral or myocardial thrombosis can result.

Thalassaemia

Thalassaemiae are a group of congenital disorders characterized by a deficient synthesis of either α- or β-chains of globin in the haemoglobin molecule, which results in microcytic and hypochromic appearance and an aberrant morphology of red blood cells.

Types

- **α-Thalassaemia:** Deficient or reduced α-chain. This condition is incompatible with life, due to lack of oxygen-carrying capacity by haemoglobin. Clinical signs in α-thalassaemia depends on the severity of the α-chain production deficiency.
- **β-Thalassaemia:** Deficient or reduced β-chain. Affected individuals are either heterozygous or homozygous. The heterozygous individual β-thalassaemia minor; the homozygous state is known as β-thalassaemia major or Cooley's anaemia.
- **β-Thalassaemia minor:** Mostly asymptomatic, suffer from mild microcytic anaemia. No treatment is needed, but genetic counselling should be offered.

β-thalassaemia major

(Synonym: Cooley's anaemia)

- It is an inherited disorder characterized by diminished synthesis of β-globin chains of haemoglobin molecule.
- It is the most severe form of congenital haemolytic anaemia.
- It is an autosomal dominant inheritance disorder.

Clinical features

- Retarded growth and development occurs.
- Delayed appearance of secondary sexual characters.
- Yellowish pallor of skin is seen.
- Pallor, jaundice and haemosiderosis are present.
- Fever, chills, malaise and weakness are common.
- Cardiomegaly, hepatomegaly and splenomegaly are seen.
- ***Oral manifestations***
 - Dental and facial abnormalities include poor spacing of teeth, a marked open bite, prominent malar bones and a saddle nose.
 - Bimaxillary protrusion and other occlusal abnormalities are frequent in thalasssemia major.

- Pneumatization of the maxillary sinuses is delayed.
- As a result of these skeletal changes, the upper lip is retracted, giving the child a *chipmunk facies*.
- Cranial nerve palsies have been described in thalassaemia due to the extramedullary haematopoiesis resulting in pressure on the nerves.
- In β-thalassaemia major, there is no correlation between the chronological, skeletal, and dental developmental age. The skeletal retardation increases with age due to hypoxia.
- Anaemia, endocrine hypofunction secondary to iron deposition, or the toxic action of iron enzyme systems leading to tissue injury.
- The high concentration of iron in enamel and dentine of deciduous and permanent teeth explains the discolouration of teeth in patients with β-thalassemia major.

Radiographic features

- *Hair-on-end* appearance of skull
- Thickening of diploe
- Osteoporosis
- Thinning of cortex
- Intraoral radiograph: *Salt and pepper effect*—due to coarsening of some trabeculae and loss of others, thin lamina dura, circular radiolucencies.

Laboratory findings

- Peripheral blood smear shows:
 - Hypochromic, microcytic anaemia
 - Poikilocytosis, anisocytosis
 - Target cells, safety pin cells
 - Nucleated RBCs
 - Heinz bodies—α-thalassemia
- WBC count elevated: 10,000–25,000 cells/mm^3
- Bone marrow smears: Hyperplasia and increased primitive cells
- Increased serum bilirubin

Prognosis and predictive factors

- Patients with mild thalassaemia (α trait or β minor) are clinically normal and require no treatment.
- With regular blood transfusions, if haemoglobin level is maintained

between 10 and 14 g/dl, the children develop normally, without any marked skeletal changes.
- The iron overload resulting with frequent blood transfusions can be treated with continuous injections of a chelator, deferiprone, which mobilizes and excretes the excess iron.
- Delayed wound healing may ensue after surgical dental procedures.

Polycythaemia or polycythaemia vera

- It is defined as an abnormal increase in the erythrocyte count in the peripheral blood, usually accompanied by an increase in haemoglobin and haematocrit.
- Three main groups of polycythaemia are recognized:
 - Primary proliferative polycythaemia (*polycythaemia vera*).
 - *Secondary polycythaemia:* It is a reactive erythrocytosis to compensate for hypoxia, usually seen in people living at high altitudes.
 - *Apparent polycythaemia:* It is characterized by an increased haemoglobin concentration and packed-cell volume, but normal RBC count is caused by a reduction in plasma volume.

Polycythaemia vera

- Polycythaemia vera (PV) is a myeloproliferative disorder characterized by excessive proliferation of erythroid elements along with granulocytic and megakaryocytic cells.
- The RBC count increases to 6 to 12 million/mm^3 with a haemoglobin concentration of 18 to 24 g/dl, leading to increased blood viscosity and thrombosis.
- 70% of cases also have high white blood cell and platelet counts.

Pathogenesis

The aetiology of PV is unknown.

Clinical features

- Cyanosis is seen on the face and extremities, due to the presence of deoxygenated blood in cutaneous vessels.
- Headache, dizziness, tinnitus and pruritus.
- Purplish red discolouration of the tongue, cheeks and lips.

- Spontaneous gingival haemorrhage
- Petechiae and ecchymoses are observed in patients with platelet abnormalities.
- Patients suffer from thrombosis and haemorrhage.

Prognosis and predictive factors

- Myelosuppressive agents.
- Chemotherapy: Busulfan, chlorambucil, cyclophosphamide and melphalan.
- Hydroxyurea also decreases the thrombotic complications.

Erythroblastosis fetalis

It is a type of congenital haemolytic anaemia due to Rh factor incompatibility resulting in destruction of fetal RBCs brought about by maternal blood antibodies.

Pathogenesis

- Inheritance of Rh positive antigen from the father by the fetus to Rh negative mother.
- The transplacental transfer of this antigen and transplacental leaks of red cells, from the fetus to the mother results in immunization of the mother and forms antibodies against it.
- These antibodies transferred back to fetus by the same route produce fetal haemolysis.

Clinical features

- It depends on severity; stillborn or alive
- Anaemia with pallor
- Jaundice
- Compensatory erythropoiesis
- Oedema
- Oral manifestations include deposition of blood pigment in the enamel and dentine of the developing teeth, giving them a green, brown or blue hue.
- *Rh hump:* It is a ring-like defect at incisal edge of anterior deciduous teeth and middle portion of first molars.

- Enamel hypoplasia is usually reported in some cases.

Laboratory findings

- RBC count: 10,00,000 to normal
- Nucleated RBC in peripheral smear
- Increased bilirubin
- *Coombs test:* Positive

Prognosis and predictive factors

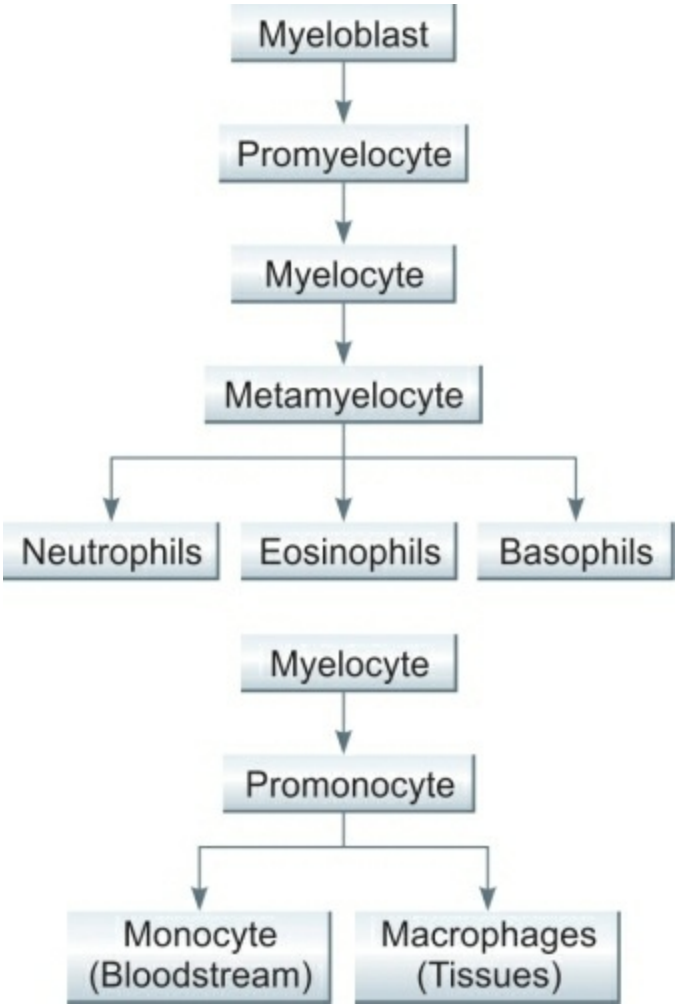
Veneers or crowns for discoloured teeth are given.

Diseases involving white blood cells

Granulopoiesis

The formation of granulocytes (neutrophils, eosinophils, basophils and monocytes) is called as granulopoiesis.

Granulopoiesis is illustrated in Flowchart 18.2.



FLOWCHART 18.2 Granulopoiesis

Leukopaenia

- It is an abnormal reduction in the number of WBCs below 4,000–4,500/mm^3 in the peripheral bloodstream.

- It is not a disease, but considered a sign of an underlying disorder.
- The causes include various infections, cachexia and debilitating states, haemopoietic states like aplastic anaemia, chemical agents, physical agents, anaphylactic shock, etc.
- It affects predominantly granulocytes. A decrease in granulocytes chiefly results from a decrease in neutrophils and most cases of leukopaenia are known as neutropenia.
- The degree of neutropenia predicts the risk of serious bacterial infections.
- Leucopenia may occur alone or as part of a generalized suppression of the bone marrow also affecting the erythrocytes and platelets (pancytopenia).

Clinical features

- The degree of neutropenia predicts the risk of serious bacterial infections.
- Decreased inflammatory response to infection.
- Most common sign is fever.
- Common sites of infection include the lungs, urinary tract, skin, rectum and mouth.
- Acute bacterial infections are the most common and usually are caused by *Staphylococcus aureus*, *Klebsiella*, *Pseudomonas* and *Proteus*.

Prognosis and predictive factors

- Broad-spectrum antibiotics
- Bone marrow transplants in severe cases

Agranulocytosis

- Agranulocytosis is an acute condition characterized by decreased number of circulating WBCs, predominantly neutrophils below 100 cells/mm^3 of blood, which is less than 5% of the normal value.
- The terms *agranulocytosis*, *granulocytopenia* and *neutropenia* are sometimes used interchangeably. But, agranulocytosis implies a more severe deficiency. Neutropenia is the term normally used to describe absolute neutrophil counts (ANC) of less than 500 cells/µl, whereas agranulocytosis is reserved for cases with ANC of less than 100 cells per microlitre.

Pathogenesis

- Drugs: Idiosyncrasy or allergic reaction to antiepileptics, antithyroid drugs, antibiotics, cytotoxic drugs, gold, NSAIDs, antidepressants and some antipsychotics.
- It may be congenital, *Kostmann syndrome.*

Clinical features

- **Age.** Any age group.
- **Sex.** Female predilection.
- **Signs and symptoms**
 - Asymptomatic in few patients
 - Fever, chills, sore throat, weakness, malaise
 - Rapidly progressing infections
 - Septicaemia
 - Regional lymphadenitis
 - ***Oral manifestations***
 - Necrotizing ulcerations of gingival or palatal mucosa, tonsils, pharynx.
 - Ragged necrotic ulcers with black or grey membrane are seen.
 - Minimal inflammatory reaction is present.
 - Pathognomonic feature includes absence of neutrophils in ulcerated areas.

Laboratory findings

- The absolute neutrophil count will be below 500 cells, and can even reach up to 0 cells/mm^3.
- Bone marrow examination shows normocellular (normal amounts and types of cells) blood marrow with underdeveloped promyelocytes.

Prognosis and predictive factors

- In asymptomatic patients, close monitoring is necessary.
- In symptomatic patients, broad-spectrum antibiotics are given.

Cyclic neutropenia

Cyclic neutropenia is a form of neutropenia that tends to occur every 3 weeks and lasting 3–6 days at a time due to changing rates of cell production by the bone marrow.

Pathogenesis

- Cyclic neutropenia is a rare, dominantly inherited disorder with mutations in ELA2, the gene encoding neutrophil elastase.
- Normal haematopoiesis is not constant in the bone marrow of patients with cyclic neutropenia, causing fluctuations in marrow platelet and erythrocyte precursors and granulocytes.

Clinical features

- **Age.** Usually, it affects in first year of life; adult onset is rare.
- **Sex.** No sex predilection.
- **Signs and symptoms**
 - Cyclical episodes of neutropenia occurring every 21 days.
 - The patient is healthy between neutropenic episodes, but at regular intervals, the absolute neutrophil count falls quickly below 500/mm^3.
 - The most common signs are fever, stomatitis, pharyngitis, and skin abscesses.
 - Lung and urinary tract infections and rectal and vaginal ulcers are seen.
 - ***Oral manifestations***
 - *Oral mucosal ulcers:* The oral ulcers recur with each new episode of neutropenia and resemble the large deep scarring ulcers seen in major aphthous stomatitis.
 - *Periodontal disease:* The periodontal manifestations range from marginal gingivitis to rapidly advancing periodontal bone loss caused by bacterial infections.

Laboratory findings

A series of three total and differential WBC counts per week for 4–6 weeks is necessary to confirm the diagnosis.

Prognosis and predictive factors

- Careful monitoring of the patient for infection during neutropenic periods and vigorous early management of infection.
- Patients require frequent dental treatment to minimize advancing periodontal disease.
- Dental treatment should be confined to the periods when the absolute neutrophil count is above 2000/mm^3. A white cell count taken in the day of a dental procedure is a wise precaution because the neutrophil count can

change rapidly.

Chediak–Higashi syndrome

- Chediak–Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by abnormal intracellular protein transport that affects multiple systems of the body.
- Patients with CHS exhibit hypopigmentation of the skin, eyes, and hair; prolonged bleeding; easy bruisability; recurrent infections; abnormal natural killer cell function; and peripheral neuropathy.

Pathogenesis

- Defect in CHS1 gene localized to bands 1q42–43.
- The CHS protein is expressed in the cytoplasm of cells of a variety of tissues and may represent an abnormality of organellar protein trafficking.
- As a result of disordered intracellular trafficking, there is impaired lysosome degranulation with phagosomes, so phagocytosed bacteria are not destroyed by the lysosome's enzymes.
- Patients with CHS exhibit alterations in neutrophils. These alterations include neutropenia, impaired chemotaxis, and impaired bactericidal activity leading to susceptibility to infections.

Clinical features

- **Age.** It appears soon after birth or in children younger than 5 years.
- **Sex.** No sex predilection.
- **Signs and symptoms**
 - Oculocutaneous albinism with photophobia, neurologic features, recurrent infections and enterocolitis.
 - Superficial skin infections, deep subcutaneous abscesses and ulcers that heal slowly and result in atrophic scars.
 - Abnormal gait, clumsiness, seizures, paraesthesia, mental retardation and peripheral neuropathy.
 - An accelerated phase of the disease with widespread infiltration by lymphocytes and histiocytes, causing rapid enlargement of the liver, the spleen, and the lymph nodes, and with concurrent severe leukopaenia and thrombocytopenia, resulting in death from infection or bleeding.
 - Death often occurs in the first decade as a result of infection, bleeding

or development of the accelerated lymphoma-like phase.

- ***Oral manifestations:*** Gingivitis, oral ulcers and periodontal disease are common findings in patients with CHS, and early loss of teeth owing to periodontal disease and caries is frequently reported.

Prognosis and predictive factors

- Allogenic bone marrow transplantation (BMT) from an HLA-matched sibling is the therapy of choice and should be performed early. Without BMT, children with CHS usually die before the age of 10 years.
- Antibiotics for infections.

Leukocytosis

- Leukocytosis is defined as white blood cell count greater than 11,000 per mm^3 (11×10^9/l) and typically reflects the normal response of bone marrow to an infectious or inflammatory process.
- A leukocyte count above 25 to 30×10^9/l is termed a *leukemoid reaction*, which is the reaction of a healthy bone marrow to extreme stress, trauma, or infection. It is different from leukaemia, in which immature white blood cells are present in peripheral blood.
- Increase in the number of white blood cells may result from infection, tissue necrosis, allergic reactions, neoplastic diseases, inflammatory diseases, or any activity, such as stress or exercise that increases epinephrine release.
- Leukocytosis can be subcategorized by the type of white blood cell that is increased in number:
 - *Neutrophilia:* Neutrophils are elevated, e.g. acute bacterial infections, tissue necrosis, myocardial infarction, burns, etc.
 - *Lymphocytosis:* Lymphocyte count is elevated, e.g. chronic infections, tuberculosis, brucellosis, viral infections like hepatitis, cytomegalovirus infection, etc.
 - *Monocytosis:* Monocyte count is elevated, e.g. chronic infections, tuberculosis, bacterial endocarditis, rickettsiosis, malaria, systemic autoimmune diseases, inflammatory bowel diseases, etc.
 - *Basophilia:* Basophil count is elevated, e.g. myeloproliferative diseases.
 - *Eosinophilia:* Eosinophil count is elevated, e.g. allergic disorders, parasitic infections, systemic autoimmune diseases, vasculitis, etc.
- The mechanism that causes leukocytosis can be of several forms:

- An increased release of leukocytes from bone marrow storage pools.
- Decreased margination of leukocytes on to vessel walls.
- Decreased extravasation of leukocytes from the vessels into tissues.
- An increase in number of precursor cells in the marrow.
- Certain medications, including corticosteroids, lithium and beta agonists, may cause leukocytosis.

- Treatment includes identification of the underlying condition and its treatment.

Infectious mononucleosis

(Synonyms: Glandular fever; Kissing disease; Pfeiffer's disease)
Infectious mononucleosis (IM) is an infectious, widespread viral disease caused by the Epstein-Barr virus (EBV).

Pathogenesis

- The only predisposing risk factor for IM is close contact with an individual infected with EBV.
- EBV is transmitted through intimate contact with body secretions, primarily oropharyngeal secretions. The infection spreads via saliva and has an incubation period of 4–7 weeks. Symptoms usually persist for 2–3 weeks, but fatigue is often more prolonged. It is thought that the most contagious period lasts about 6 weeks after the onset of symptoms.
- Initially virus replicates within the epithelial cells of pharynx, which causes pharyngitis, and infects the B lymphocytes in the oropharyngeal epithelium. Circulating B cells spread the infection throughout the entire reticular endothelial system (RES), i.e. liver, spleen and peripheral lymph nodes. EBV infection of B lymphocytes results in a humoral and cellular response to the virus.
- The humoral immune response directed against EBV structural proteins is the basis for the test used to diagnose EBV infectious mononucleosis.
- The T lymphocyte cellular response is critical in determining the clinical expression of EBV infection. A rapid and efficient T cell response results in control of the primary EBV infection and lifelong suppression of EBV.

Clinical features

- **Age.** Younger age group.
- **Sex.** No sex predilection.

- **Signs and symptoms**
 - Most of the patients are asymptomatic.
 - Triad of fever, pharyngitis, and lymphadenopathy is seen.
 - Early signs include sore throat, fever, fatigue, weight loss, photophobia, malaise, pharyngeal inflammation, vomiting, petechiae and loss of appetite.
 - Tonsillar enlargement, lymphadenopathy, splenomegaly, hepatomegaly and jaundice are seen.
 - Rarely thrombocytopenia, splenic rupture and haemolytic anaemia are seen.

Laboratory findings

- Clinical presentation of classical triad of fever, pharyngitis and lymphadenopathy.
- Monospot test is positive only in 50% of cases.
- IgG and IgM antibody tests are more specific.

Prognosis and predictive factors

- IM is generally self-limiting and only symptomatic treatment is used.
- Closely monitor patients with extreme tonsillar enlargement for airway obstruction. Steroids are indicated for impending or established airway obstruction.
- Surgery is necessary for spontaneous splenic rupture.

Leukaemia

- Leukaemia is a malignant neoplasm characterized by a proliferation of abnormal white blood cells within the bone marrow.
- There is a failure of maturation of precursor cells (blasts) with the result that the blasts accumulate in the marrow and suppress normal haematopoietic stem cells.
- As the number of malignant white blood cells developing in the marrow increases, they rapidly enter the circulation.
- Despite an increase in the white blood cell count, the leukaemic leukocytes are non-functional. The resulting paucity of functional white cells, red cells and platelets is responsible for immunodeficiency, anaemia and thrombocytopenia, respectively.

Classification

- The leukaemiae are subdivided into *chronic* and *acute forms.*
- Chronic leukaemiae involve relatively well-differentiated leukocytes, are slow in onset and run an indolent course.
- Acute leukaemiae are characterized by an uncontrolled proliferation of poorly differentiated blast cells. They are abrupt in onset, aggressive and rapidly fatal, if left untreated. Oral manifestations are more common in acute leukaemiae.
- Chronic and acute leukaemiae are classified according to the type of white blood cell involved, i.e. *lymphoid* and *myeloid,* as follows:
 - Acute lymphoblastic leukaemia (ALL)
 - Acute myeloblastic leukaemia (AML)
 - Chronic lymphoblastic leukaemia (CLL)
 - Chronic myeloblastic leukaemia (CML)
- Both acute lymphoid leukaemia and acute myeloid leukaemia are further subdivided within the French–American–British (FAB) classification according to their degree of differentiation along cell lines and extent of cell maturation.

Revised FAB classification of acute leukaemiae

- **Acute myeloblastic leukaemia**
 - M0: Minimally differentiated AML
 - M1: AML without maturation
 - M2: AML with maturation
 - M3: Acute promyelocytic leukaemia
 - M4: Acute myelomonocytic leukaemias (Naegeli type)
 - M5: Acute monocytic leukaemia (Schilling type)
 - M6: Acute erythroleukaemia (Di Guglielmo's syndrome)
 - M7: Acute megakaryocytic leukaemia
- **Acute lymphoblastic leukaemia**
 - L1: Childhood-ALL (B-ALL and T-ALL)
 - L2: Adult-ALL (mostly T-ALL)
 - L3: Burkitt type-ALL (B-ALL)

Pathogenesis

- The causes of leukaemia are poorly defined. However, following factors have been implicated:

- **Genetic factors:** Acute leukaemias occur with increased frequency with a variety of congenital disorders such as Down's, Bloom's, Klinefelter's and Wiskott–Aldrich syndromes, Fanconi anaemia and ataxia telangiectasia.
- **Environmental factors**
 - *Ionizing radiation:* Individuals exposed to occupational radiation exposure, patients receiving radiation therapy and atomic bomb explosions. Radiation exposure is related to the development of CML, AML and ALL but not to CLL.
 - *Chemical carcinogens:* Benzene and other aromatic hydrocarbons are associated with the development of AML.
 - *Drugs:* Alkylating agents and other chemotherapeutic agents are associated with increased incidence of AML.
- **Infection:** Retrovirus, human T cell leukaemia-lymphoma virus-I (HTLV-I) and HTLV-II may be causative agents for ALL.

- Leukaemia arises following *malignant transformation of a single clone cells belonging to myeloid or lymphoid series, followed by proliferation of the transformed clone.*
- The salient features in the pathogenesis of leukaemiae are as follows:
 - In acute leukaemia, the single most prominent characteristic of the leukaemic cells is a defect in maturation beyond the myeloblast or promyelocyte level in AML, and the lymphoblast level in ALL. However, it may be emphasized here that it is the *maturation defect* in leukaemic blasts rather than rapid proliferation of leukaemic cells responsible for causing acute leukaemia.
 - The leukaemic cells proliferate primarily in the bone marrow, circulate in the blood and *infiltrate into other tissues* such as lymph nodes, liver, spleen, skin, viscera and CNS.
 - The *mechanism of leukaemic transformation* is poorly understood. But the defect lies in the DNA, conferring a heritable malignant characteristic to the transformed cell and its progeny. A neoplastic phenotype may be induced by RNA viruses (e.g. HTLV-I) and causes insertional mutagenesis for which oncogenes may play an important role. A number of clonal cytogenetic abnormalities have been reported in association with the various forms of acute and chronic leukaemiae. The most consistent chromosomal abnormalities among these is Philadelphia (Ph) chromosome seen in 70–90% cases with CML, involving reciprocal translocation of parts of long arm of chromosome

22 to the long arm of chromosome 9, i.e. t(9;22).

- As the leukaemic cells accumulate in the bone marrow, they *suppress normal haematopoietic stem cells,* partly by physically replacing the normal marrow precursors.

Clinical features

Clinical features of leukaemias are illustrated in Table 18.1.

Table 18.1

Clinical features of leukaemia

Type	Affected group	Clinical features	Oral manifestations	Diagnosis
ALL	Children	Fever is an early sign of disease owing to recurrent infections of the lungs, urinary tract, skin, mouth, rectum and upper respiratory tractInfiltration of organs and tissues by leukaemic cells causes lymphadenopathy, hepatomegaly, and splenomegaly Cells may infiltrate the central nervous system or peripheral nerves, leading to cranial nerve palsy, paraesthesia, anaesthesia, and paralysis Localized tumours consisting of leukaemic cells are called *chloromas*. The surface of these tumours turns green when exposed to light because of the presence of myeloperoxidase	Gingival hyperplasia, oral ulceration, spontaneous gingival bleeding, petechiae, mucosal pallor, lymphadenopathy, tonsillar swelling, paraesthesia due to leukaemic infiltration of fifth and seventh cranial nerves and fungal infections	Significant number of immature granulocytic or lymphocytic precursors are present in the peripheral blood, along with significant anaemia and thrombocytopeniaMicroscopic examination of a bone marrow aspirate confirms the diagnosis
AML	Adults			
CML	30–50 years	Bone marrow infiltration causes anaemia and thrombocytopenia, resulting in pallor, weakness, dyspnoea, and purpura; infiltration of other tissues causes lymphadenopathy, splenomegaly, hepatomegaly, and leukaemic infiltrates of skin or mucosa	Tonsillar enlargement, cervical lymphadenopathy, oral bleeding, leukaemic infiltrates in gingiva, palate, alveolar bone, dental pulp, infections and oral ulcers	Presence of thePhiladelphia chromosome in 90% of cases and the absence of leukocyte alkaline phosphatase
CLL	40–60 years			Peripheral blood smear, bone marrow aspiration

Prognosis and predictive factors

Treatment for oral manifestations includes:

- **Gingival haemorrhage:** Removal of obvious local irritants, direct pressure, absorbable gelatin or collagen sponges, topical thrombin, or the placement of microfibrillar collagen held in place by packing or splints, oral rinses of tranexamic acid or aminocaproic acid. If these local measures are not successful, platelet transfusions are necessary.
- **Oral ulcers:** The ulcers are characteristically large, irregular, and foul smelling, and are caused by recurrent HSV infection. The lesions respond well to parenteral acyclovir administered intravenously. The ulcers in

hospitalized leukaemic patients taking chemotherapy may be infected with gram-negative enteric bacilli. Topical antibacterial treatment can be attempted with povidone-iodine solutions, bacitracin-neomycin ointments or chlorhexidine rinses. Kaolin and pectin plus diphenhydramine oral rinses can be used to reduce pain.

- **Oral infections:** Intravenous broad-spectrum antibiotics for bacterial infections. Antifungal agents for commonly occurring fungal infections.

Diseases involving platelets

Thrombopoiesis

- Platelets are formed in the bone marrow by a process of fragmentation of the cytoplasm of megakaryocytes.
- Platelet production appears to be under the control of thrombopoietin.
- The stages of platelet production are:
 - **Megakaryoblast:** It arises from haematopoietic stem cell by a process of differentiation.
 - **Promegakaryocyte:** A megakaryoblast undergoes endo-reduplication of nuclear chromatin, i.e. nuclear chromatin replicates repeatedly in multiples of two division of the cell. Ultimately, a large cell containing up to 32 times the normal diploid content of nuclear DNA (polyploidy) is formed when further nuclear replication ceases and cytoplasm becomes granular.
 - **Megakaryocyte:** A mature megakaryocyte is a large cell, 30–90 μm in diameter and contains 4–16 nuclear lobes having coarsely clumped chromatin. The cytoplasm is abundant, light blue in colour and contains red-purple granules. Platelets are formed from pseudopods of megakaryocyte cytoplasm which get detached into the bloodstream. Each megakaryocyte may form up to 4000 platelets. The formation of platelets from the stem cell takes about 10 days.
 - **Platelets:** Platelets are small (1–4 μm in diameter), discoid, non-nucleate structures containing red-purple granules. The normal range of platelets is 1,50,000–4,00,000 cells/mm^3 blood in a healthy individual and its lifespan is 7–10 days.

Thrombocytopenia

Thrombocytopenia is a bleeding disorder characterized by low platelet counts, i.e. below 1,50,000 cells/mm^3 blood.

Pathogenesis

- *Inadequate production of platelets:* Defective maturation of platelets is due to cytotoxic drugs, bone marrow irradiation or replacement, aplastic anaemia, vitamin B_{12}/folic acid deficiencies.

- *Disordered platelet destruction:* It includes stasis of circulating platelets in spleen, splenomegaly.
- *Increased platelet destruction:* The survival rate of platelets is reduced by the antibodies as in autoimmune thrombocytopenic purpura, pregnancy and blood transfusions, drugs, infection, collagen disorders and allergies.

Types

- *Primary or idiopathic thrombocytopenia:* When the platelet counts are reduced due to unknown causes.
- *Secondary thrombocytopenia:* Systemic diseases, chemicals or radiation have a direct effect on the bone marrow and reduce the platelet count.

Clinical features

- Often, the first manifestations are in oral cavity.
- Most common clinical signs are petechiae and ecchymoses.
- Other signs include epistaxis, haematuria, hypermenorrhoea and gastrointestinal bleeding.
- Multifocal palatal petechiae and ecchymoses are present intraorally.
- The petechiae do not blanch on pressure.
- Palate is the most common site.
- Gingival haemorrhage is the hallmark of the disease, and is often spontaneous and persistent.
- Often, haemorrhage starts in sulcus area and turns to purplish black clots which adhere to oral structures.
- The patients often have a mouth odour characteristic of 'fresh blood'.
- At times, patients experience nausea due to swallowing moderate to large quantities of blood.
- Spontaneous haemorrhage after tooth brushing or minor trauma.
- Haemorrhaging on the buccal mucosa at the occlusal line due to cheek biting.

Laboratory findings

They include decreased platelet count, increased bleeding time, prothrombin time and partial thromboplastin time.

Prognosis and predictive factors

- Treatment is directed at reducing the level and source of autoantibodies

and reducing the rate of destruction of sensitized platelets. This is possible by corticosteroid therapy, immunosuppressive drugs (e.g. vincristine, cyclophosphamide and azathioprine) and splenectomy.
- Platelet transfusions are helpful as a palliative measure only in patients with severe haemorrhage.

Primary thrombocytopenia

(Synonyms: Idiopathic thrombocytopenic purpura; autoimmune thrombocytopenic purpura [AITP])

It is one of the most common autoimmune diseases affecting both adults and children.

Pathogenesis

- In many cases, the cause is not idiopathic but autoimmune, with antibodies against platelets being detected in approximately 60% of patients.
- These antibodies are of IgG type and act against platelet membrane glycoproteins IIb-IIIa or Ib-IX, and they reduce the platelet count by:
 - IgG coats the platelets and makes them susceptible to phagocytosis by splenic macrophages and Kupffer's cells in the liver.
 - Damage megakaryocytes, which are the precursor cells to platelets.

Types

- *Acute AITP:* It occurs mostly in children, characterized by episodes of sudden onset of bleeding followed by a viral or respiratory illness. The disease lasts for few weeks and has a high recovery rate.
- *Chronic AITP:* It commonly affects young women. No association with viral infection or respiratory illness and characterized by easy bruisability.

Clinical features

- Abrupt appearance of petechial haemorrhages, purpura (macular haemorrhages) and bruising immediately after trauma are seen.
- The petechial haemorrhages can cover large areas and appear like rash, which does not itch or pain.
- Bleeding from the nostrils, bleeding at the gums, and menorrhagia (excessive menstrual bleeding), any of which may occur, if the platelet count is below 20,000 per μl.

- A very low count (<10,000 per μl) may result in the spontaneous formation of haematomas in the oral mucosa and other mucous membranes.
- Bleeding time from minor lacerations or abrasions is usually prolonged.
- Serious and possibly fatal complications due to an extremely low count (<5000 per μl) and may include subarachnoid or intracerebral haemorrhage, lower gastrointestinal bleeding or other internal bleeding.
- An AITP patient with an extremely low count is vulnerable to internal bleeding caused by blunt abdominal trauma.
- In approximately 1% of cases, autoimmune haemolytic anaemia and ITP coexist, a condition referred to as *Evan's syndrome.*

Laboratory findings

- The diagnosis of AITP is a process of exclusion.
- No blood abnormalities other than low platelet count and no physical signs except for signs of bleeding.
- Increase in the production of megakaryocytes in the bone marrow examination helps in establishing a diagnosis of AITP.

Prognosis and predictive factors

- Treatment depends on patient's age and severity of spontaneous haemorrhage, cause and natural history of the disease.
- Approximately, 80% of children with acute AITP recover in 6–12 weeks regardless of the treatment.
- Treatment usually is initiated with intravenous corticosteroids, such as prednisone. Corticosteroids are used to treat children, if not recovered in 3 months, adults with chronic AITP and those with platelet counts below 20,000 cells/mm^3.

Secondary thrombocytopenia

- Drugs, radiation and various systemic diseases may have a direct effect on the bone marrow and result in secondary thrombocytopenia.
- *Common drugs associated with thrombocytopenia are:*
 - Myelosuppressive drugs used in cancer treatment
 - Immunodestructive agents
 - Quinidine
 - Cephalosporins
 - Quinine

 - Chemotherapeutic agents
 - Heparin
 - Oestrogen
 - Carbamazepine
 - Ibuprofen
 - Cimetidine
 - Tamoxifen
 - Ranitidine
 - Phenytoin
- Treatment requires stopping the drug, and administering a steroid course. Platelet counts usually return to normal within 2–3 weeks after the drug has been discontinued.
- *Systemic conditions causing thrombocytopenia are:*
 - Disseminated intravascular coagulation
 - Thrombotic thrombocytopenic purpura
 - Leukaemia
 - Infectious mononucleosis
 - HIV
 - Aplastic anaemia:
 - Vitamin B_{12} deficiency
 - Folic acid deficiency

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder characterized by thrombocytopenic purpura, haemolytic anaemia, renal failure, neurologic dysfunction and fever.

Pathogenesis

Patients with TTP have unusually large multimers of von Willebrand factor (vWF) in their plasma and they lack a plasma protease that is responsible for the breakdown of these ultra-large vWF multimers. In the congenital form of TTP, mutations in the gene encoding this protease have been described. In the more common sporadic form, an antibody inhibitor can be isolated in most patients. This protease has been isolated and cloned and is designated ADAMTS13.

Clinical features

- No significant racial and sexual predilection, often affects middle-aged people.
- TTP can affect any organ system, but involvement of the peripheral blood, the central nervous system, and the kidneys causes the clinical manifestations.
- The most common presentation is petechiae and neurologic symptoms. The neurologic symptoms can range from headache and confusion to seizures and coma.
- Fever is present in slightly more than 50% of the patients.
- Precipitating factors include pregnancy, infection, SLE, drugs like penicillamine, sulphonamides and oral contraceptives.
- The classic histologic lesion comprises a thrombus formation with predominantly platelets, little fibrin and RBCs.
- Patients with TTP have abnormally shaped RBCs, anaemia with haemoglobin less than 6 mg/dl, negative Coombs' test, normal PT, slightly prolonged thrombin time and platelet count in the range of 10,000–50,000 cells/mm^3.

Prognosis and predictive factors

- Untreated, TTP has a mortality rate of as high as 90%. With plasma exchange, the mortality rate is reduced to 10–20%.
- Acute morbidities include ischaemic events such as stroke, transient ischaemic attacks, myocardial infarction and arrhythmia, bleeding, and azotaemia.

Thrombocythaemia

Thrombocythaemia is a myeloproliferative blood disorder characterized by excessive production of platelets in the bone marrow.

Pathogenesis

Idiopathic: The exact aetiology is unknown.

Clinical features

- It affects both women and men of all ethnic backgrounds.
- It may occur at any age but tends to be more common in adults.
- Erythema, burning or itching skin.

- Mildly enlarged spleen.
- Headache, dizziness, weight loss.
- Abnormal bleeding (rarely).
- Pregnancy complications.
- Most frequently encountered problem is abnormal blood clotting.

Laboratory findings

- Thrombocythaemia may be diagnosed from a blood test during a routine physical examination.
- An abnormally high number of platelets will be detected in the blood.
- Physical examination reveals an enlarged spleen.
- Bone marrow biopsy.

Prognosis and predictive factors

- Treatment depends on the level of platelets in the blood and the risk of clotting or bleeding complications.
- Platelet pheresis (removing platelets from the blood) may be used as an emergency treatment to quickly reduce an extremely high platelet level.
- Those with higher risk may be treated with medications such as *hydroxyurea*, *anagrelide* or *interferon alpha*.
- Individuals with essential thrombocythaemia usually have a normal lifespan with proper medical treatment. However, stroke, heart attack or other serious complication can cause disability.

Haemophilia A

Haemophilias are a group of inherited diseases characterized by deficiency of clotting factors.

Types

- *Haemophilia A* or *classic haemophilia:* It is an inherited X-linked, recessive disorder caused by deficiency of clotting factor VIII. It makes up to approximately 80% of haemophilia cases.
- *Haemophilia B:* It is caused due to deficiency of factor IX. In 1952, Christmas disease was described and named after *Stephen Christmas*, the first patient who was examined in detail.
- *Haemophilia C:* It is caused due to deficiency of factor XI. Predominantly

affects Ashkenazi Jews and shows autosomal inheritance.

Hemophilia A

- Deficiency of antihemophilic factor or factor VIII is called haemophilia.
- It is an inherited, X-linked recessive disorder characterized by excessive haemorrhage due to a prolonged clotting time.
- The males are clinically affected and females are carriers.
- Haemophilia is one of the oldest described genetic diseases. The gene for factor VIII is located on the long arm of chromosome X.
- Inversions, deletions, insertions and point mutations account for the genetic defects that are associated with deficiency of factor VIII.

Classification

The classification of haemophilia A is based on the severity and plasma antihemophilic globulin (AHG) levels (Table 18.2).

Table 18.2

Classification of haemophilia A

Type	Clotting factor level	Age group	Bleeding tendency
Severe	1%	<1 year	Spontaneous bleeding, predominantly in joints and muscles
Moderate	1–5%	1–2 years	Occasional spontaneous bleeding; severe bleeding with trauma and surgery
Mild	5–40%	>2 years	Severe bleeding with major trauma or surgery

Clinical features

- **Age.** Younger age group.
- **Sex.** Males are affected and females will be carriers.
- **Signs and symptoms**
 - Spontaneous haemorrhage into joints is the hallmark of the disease.
 - Repeated episodes result in deformity of the joint.
 - Haemorrhage into subcutaneous tissues, internal organs and muscles.
 - Easy bruising.
 - Poor wound healing and abnormal scar formation.
 - Bleeding in soft tissue.

- Persistent bleeding after surgery.
- Persistent bleeding after tooth extraction.
- Gingival bleeding in response to slight trauma.

Laboratory findings

- Clotting time is prolonged.
- Bleeding time, platelet count and prothrombin time are normal.

Prognosis and predictive factors

- Haemophilia is primarily treated by replacing the absent or abnormal clotting factors to prevent severe blood loss and complications from bleeding.
- Prophylactic administration of clotting factor concentrates is advisable prior to engaging in activities with higher risk of injury to prevent bleeding.

Dental considerations

People with haemophilia or congenital bleeding tendencies are a priority group for dental and oral health care, since bleeding after dental treatment may cause severe or even fatal complications. Maintenance of a healthy mouth and prevention of dental problems is of greater importance in preventing future complications.

- People with haemophilia should be educated on good oral hygiene right from a young age to prevent the occurrence of gingival and periodontal disease.
- Dental appointments for children with bleeding disorders should be started when the deciduous teeth begin to erupt.
- For people with mild or moderate haemophilia, non-surgical dental treatment can be started after giving antifibrinolytic agents (tranexamic acid or epsilon aminocaproic acid), but a haematologist must be consulted before other procedures are done.
- For those with severe haemophilia, factor VIII replacement is necessary before surgery or regional nerve block injections or scaling.
- Extractions should be as atraumatic as possible.
- Bleeding can be aggravated by analgesics such as ASA or other NSAIDs such as indomethacin. Paracetamol/acetaminophen and codeine are safe alternative analgesics.

- Antibiotic prophylaxis should be administered to patients with prosthetic joint replacements.
- Intraligamentary injection is safe to use as it does not cause haemorrhage.

Von Willebrand disease

- von Willebrand disease (vWD) is the most common bleeding disorder described in humans and is caused by a deficiency of a blood clotting protein, called von Willebrand factor.
- The disease is estimated to occur in 1 to 2% of the population and is first described by *Erik von Willebrand*.
- vWD subtypes I and II are usually inherited in an autosomal dominant pattern and subtype III is inherited as an autosomal recessive type.
- von Willebrand factor is a protein critical to the initial stages of blood clotting and it circulates attached to factor VIII. This glue-like protein interacts with platelets to form a plug and is responsible for platelet adhesion to subendothelium.

Clinical features

- Recurrent nose bleeds (epistaxis) are a hallmark of this disease.
- Excessive bleeding following minor trauma.
- Common sites of bleeding are nose, skin and gingiva.
- Post-extraction bleeding.
- Ecchymoses.
- Haemarthrosis.

Laboratory findings

- Increased bleeding time, normal platelet count, impaired adherence of platelets, decreased levels of factor VIII.
- Low AHG levels.
- Platelet count and prothrombin consumption are normal.
- Clotting time is normal.
- Capillary fragility is increased.

Prognosis and predictive factors

- Desmopressin acetate, a nasal spray, is the treatment of choice for mild von Willebrand disease.

- For excessive bleeding, infusions of a factor VIII concentrate rich in von Willebrand factor.
- Aspirin is contraindicated as it interferes with the platelet function. These patients can be given acetaminophen for pain relief.

Key points

- *Anaemia* is defined as an abnormal reduction in number of circulating red blood cells, the quantity of haemoglobin and the volume of packed red cells in a given unit of blood per age, sex and altitude of the individual.
- *Iron-deficiency anaemia:* Pallor, koilonychia, brittle nails, glossitis, glossodynia, angular cheilitis and Plummer–Vinson syndrome.
- *Pernicious anaemia* is a megaloblastic anaemia that occurs due to vitamin B_{12} deficiency, which shows Hunter's glossitis, glossodynia, dysphagia, altered taste sensation, aphthous ulcerations and burning mouth sensation.
- *Aplastic anaemia* is a pancytopenia (anaemia, leucopenia and thrombocytopenia) resulting from aplasia of bone marrow.
- *Haemolytic anaemiae* are group of anaemiae which result from decreased survival rate of erythrocytes due to intracorpuscular defects or from extracorpuscular factors.
- *Sickle cell anaemia* is an autosomal recessive disorder characterized by a replacement of glutamic acid by valine in position 6 of β-chain.
- *Thalassaemiae* are a group of congenital disorders characterized by a deficient synthesis of either α- or β-chains of globin in the haemoglobin molecule, which results in microcytic, hypochromic appearance and an aberrant morphology of red blood cells.
- *Polycythaemia* is an abnormal increase in erythrocyte count in the peripheral blood.
- *Erythroblastosis fetalis* is a congenital haemolytic anaemia due to Rh factor incompatibility resulting in destruction of fetal RBCs brought about by maternal blood antibodies.
- *Agranulocytosis* is an acute condition characterized by decreased number of circulating WBCs, predominantly neutrophils below 100 cells/mm^3 of blood.
- *Cyclic neutropenia* is a form of neutropaenia that tends to occur every three weeks and lasting three to six days at a time due to changing rates of cell production by the bone marrow.

- *Chediak–Higashi syndrome* is a rare autosomal recessive disorder characterized by abnormal intracellular protein transport that affects multiple systems of the body.
- *Leukaemia* is a malignant neoplasm characterized by a proliferation of abnormal white blood cells within the bone marrow.
- *Thrombocytopenia* is a bleeding disorder characterized by low platelet counts, i.e. below 1,50,000 cells/mm^3 blood.
- *Thrombotic thrombocytopenic purpura* is a rare disorder characterized by thrombocytopenic purpura, haemolytic anaemia, renal failure and neurologic dysfunction.
- *Thrombocythaemia* is a myeloproliferative blood disorder characterized by excessive production of platelets in the bone marrow.
- *Haemophilia A (Classic haemophilia):* Deficiency of clotting factor VIII.
- *Haemophilia B (Christmas disease):* Deficiency of factor IX.
- *Haemophilia C:* Deficiency of factor XI.

Frequently asked questions

1. Classify anemia and write about pathogenesis, clinical features and laboratory findings of iron-deficiency anaemia.
2. Plummer–Vinson syndrome.
3. Write about pathogenesis, clinical features and investigatory findings of pernicious anaemia.
4. Aplastic anaemia.
5. Haemolytic anaemia.
6. Sickle cell anaemia.
7. Discuss pathogenesis, clinical features and laboratory investigations of thalassaemia or β-thalassaemia major or Cooley's anaemia.
8. Agranulocytosis.
9. Cyclic neutropenia.
10. Chediak–Higashi syndrome.
11. Infectious mononucleosis.
12. Classify leukaemiae and discuss about pathogenesis and clinical features of acute myeloblastic leukaemiae.
13. Thrombocytopenia.
14. Haemophilia A.
15. von Willebrand disease.

CHAPTER 19

Diseases of the nerves and muscles

Diseases of nerves

Trigeminal neuralgia

(Synonyms: Fothergill's disease; Tic douloureux)

- Neuralgia is defined as the pain along the pathway of the nerve. The term *trigeminal neuralgia* means *pain along the distribution of the trigeminal nerve.*
- It is described as a sudden, sharp, lancinating, electric shock-like recurrent pain in the distribution of one or more branches of the trigeminal nerve.
- Trigeminal neuralgia (TN) is the most frequently occurring nerve pain disorder. It has one of the highest suicidal rates and is often described as 'the most terrible pain known to humans'.
- TN was first described by John Fothergill in 1773.
- TN is also called *tic douloureux* because of the characteristic muscle spasm that typically accompanies the pain attack.

Types

The International Headache Society (IHS) has identified two types of TN:
1. Classical TN
2. Symptomatic TN

Pathogenesis

Classical TN

- It is also known as *idiopathic TN,* typically caused by a blood vessel (usually the superior cerebellar artery) compressing the trigeminal nerve as it exits the brainstem. The constant compression leads to the loss of myelin sheath, the covering which surrounds the nerve fibres. The loss of the protective nerve covering is called *demyelination*. Without proper insulation, the nerve cells become hyperexcitable and begin to fire in an erratic and disorganized manner resulting in significant pain. This is believed to be the cause of 90% cases of TN.

Symptomatic TN

It includes all cases of TN secondary to an underlying, demonstrable medical

condition not related to vascular compression. The causes could be:

- Multiple sclerosis: An autoimmune disease caused by demyelination of nerve fibres in brain and spinal cord. Approximately, 3–5% of patients with TN suffer from multiple sclerosis. The patients are usually younger and have bilateral presentation.
- Other diseases which cause damage to myelin sheath-like leukodystrophy, chronic inflammatory demyelinating disease, Guillan-Barre syndrome, etc.
- A tumour compressing the trigeminal nerve.
- Abnormalities at the base of the skull.
- Arteriovenous malformations.

Approximately, 5–10% cases of TN are caused by any of these medical conditions.

Clinical features

- **Age.** 50–70 years.
- **Gender.** Female predilection.
- **Location.** The maxillary and mandibular branches are more commonly affected. The pain may be felt in the ear, eye, lips, nose, scalp, forehead, cheeks, teeth, or jaw and side of the face.
- **Signs and symptoms**
 - Solitary involvement of ophthalmic branch is seen in less than 5% of cases.
 - Pain is usually unilateral, affects right side more than left side.
 - *Triggers:* Many patients describe a specific event (trigger) that may precipitate an attack. The triggers include chewing, talking, swallowing, brushing teeth, face washing, shaving, cool breeze across the face, light touch or vibration.
 - *Trigger zones:* The pain attack is initiated by touching specific areas on the face. These are known as trigger zones and are present on ala of the nose, cheeks, vermilion of the lips, around the eyes, skin on chin, forehead, midface, alveolar bone, etc.

Diagnosis

- TN is a clinical diagnosis based on the patient's description of facial pain. There is no specific diagnostic test to confirm TN.
- The diagnostic criteria for classical TN as given by IHS guidelines are:
 - Paroxysmal attacks of pain with abrupt onset and termination, lasting

from a fraction of 1 second to 2 minutes, affecting one or more divisions of the trigeminal nerve.
 - At least one of the following characteristics of the pain:
 - Pain must be intense, sudden and sharp. Pain must be precipitated by a trigger.
 - Following an attack, there is usually a 'refractory period' in which the pain cannot be triggered.
 - Attacks must be similar in an individual patient.
 - No other identified causes of facial pain should be present.
- The diagnostic criteria for symptomatic trigeminal neuralgia are similar to the criteria for classical TN except for the following changes:
 - There may or may not be persistent aching of the face between attacks.
 - A cause for TN can be identified (excluding vascular compression) by special examinations or in exploratory surgery of the posterior fossa (the internal base of the skull).
 - There may be neurologic deficit.
 - There is no refractory period between attacks.

Prognosis and predictive factors

- Early diagnosis and appropriate treatment helps in controlling the progression of the disease as well as lesser side effects due to less dosage of medication.
 - *Medical*
 - *Anticonvulsants*
 - First-line drug—carbamazepine
 - Second-line drugs—oxocarbazepine, gabapentin, lamotrigine, phenytoin
 - *Surgical*
 - Microvascular decompression
 - Radiofrequency thermocoagulation
 - Retrogasserian glycerol injections
- TN is not a life-threatening illness. Some patients experience a remission of pain lasting many years, while for others, the symptoms intensify. Initially, most patients respond to medication, but over time, medication becomes less effective. When the pain becomes intractable or interferes significantly with daily activity, surgical options can be explored.

Glossopharyngeal neuralgia

- Glossopharyngeal neuralgia (GPN) is characterized by electric shock-like pain in the area of distribution of the ninth cranial nerve, the glossopharyngeal nerve.
- It is in every way similar to trigeminal neuralgia except for the distribution of the pain and the customary site of the triggering stimulus.

Pathogenesis

The vast majority of patients with GPN are thought to have an artery compressing the nerve as it exits from the medulla and travels through the subarachnoid space to the jugular foramen.

Clinical features

- Excruciating pain in the region of the ear, throat, tonsillar fossa, pharynx or base of the tongue.
- It can radiate to the ear or the angle of the jaw or into the upper lateral neck.
- The pain occurs in episodes and may be severe. It is usually on one side, and feels jabbing. The episodes can occur many times each day, and awaken the person from sleep.
- The trigger zone is often in the same area, and patients frequently report that swallowing, yawning, chewing, coughing, laughing, speaking or clearing the throat could be the precipitating stimulus.
- Often the pain appears to be spontaneous. Chewing or touching the face does not precipitate an attack.

Diagnosis

- The nature of the pain, its description by the patient and the chronology of the attacks are identical to those of tic douloureux of the trigeminal nerve.
- The diagnosis can be confirmed by the cessation of pain when this nerve is blocked at the jugular foramen or when topical anaesthesia of the pharynx stops the pain.

Prognosis and predictive factors

- The pharmacologic management is the same as that for tic douloureux of

the trigeminal nerve.
- When medical management fails, suboccipital craniectomy with exploration of the glossopharyngeal nerve is indicated.

Bell's palsy

(Synonym: Idiopathic facial paralysis)

- Bell's palsy is named after Sir Charles Bell, a nineteenth century Scottish anatomist who was the first to describe the condition in detail.
- Bell's palsy is defined as an idiopathic unilateral facial nerve paralysis, usually self-limiting. The hallmark of this condition is a rapid onset of partial or complete paralysis that often occurs overnight. In rare cases (1%), it can occur bilaterally resulting in total facial paralysis.

Pathogenesis

- Several conditions cause paralysis of the facial nerve, e.g. Ramsay Hunt syndrome, brain tumour, stroke, acute and chronic otitis media, Lyme disease, neurosarcoidosis, temporal bone fractures, Moebius syndrome, tumours compressing the facial nerve-like parotid gland neoplasms, haemangiomas, etc.
- Recent studies suggest that Bell's palsy could be a polyneuritis with possible viral, inflammatory, autoimmune, and ischaemic aetiologies. Increasing evidence implicates herpes simplex virus type 1 (HSV-1) and herpes zoster virus reactivation from cranial nerve ganglia.
- The various risk factors suggested for reactivating the virus are:
 - Exposure to cold
 - Sudden changes in atmospheric pressure
 - Emotional stress
 - Trauma
 - Metabolic disorders
- The exact pathophysiology is still unknown.
- It is thought that as a result of inflammation and oedema of the facial nerve, pressure is produced on the nerve where it exits from the skull within its bony canal, which may block the transmission of neural signals or damage the nerve and the nerve conductive properties are impaired.
- A recent study proposed a hypothesis that the HSV-1 infection is associated with demyelination of nerves. Demyelination may not be directly caused by the virus, but an unknown immune system causes

virus reactivation. It is stated that HSV-1 replication itself is not responsible for the damage to the facial nerves because treatment with acyclovir does not prevent the progression of nerve dysfunction.

Clinical features

- **Age.** Older age group.
- **Sex.** Female predilection.
- **Signs and symptoms**
 - Familial inheritance has been found in 4–14% of cases.
 - Pregnant women and diabetics are more at risk to get affected by Bell's palsy.
 - Sudden weakness or paralysis on one side of the face that causes it to droop.
 - Dropping of angle of mouth on the affected side and salivary drooling.
 - Inability to raise eyebrow on affected side.
 - Inability to close the eye on affected side.
 - Excessive tearing or dry eye.
 - Eyeball rolls upwards when attempted to close the eye, this is called *Bell's phenomenon.*
 - Loss of ability to taste.
 - Pain in or behind the ear.
 - Numbness in the affected side of face.
 - Patients have a '*mask-like*' or '*expressionless*' face, when they attempt to smile.

Diagnosis

- Bell's palsy is a diagnosis of exclusion, by elimination of other reasonable possibilities.
- The diagnosis is made based on the history, clinical presentation and a thorough physical examination to examine upper and lower facial weakness. There is no specific laboratory test to confirm diagnosis of the disorder.
- Electromyography (EMG) is used to confirm the presence of nerve damage and determine the severity and the extent of nerve involvement.

Prognosis and predictive factors

- Some cases are mild and do not require treatment as the symptoms

usually subside on their own within 2 weeks.

- Medical treatment includes corticosteroids like prednisone with potent anti-inflammatory function. Analgesics such as aspirin, acetaminophen or ibuprofen may relieve pain.
- Eye protection—lubricating eye drops, such as artificial tears or eye ointments or gels and eye patches are effective.
- Physiotherapy to stimulate the facial nerve and help maintain muscle tone may be beneficial to some individuals.
- Other therapies that may be useful for some individuals include relaxation techniques, acupuncture, electrical stimulation, biofeedback training and vitamin therapy (including vitamin B_{12}, B_6 and zinc), which may help restore nerve function.
- The prognosis for individuals with Bell's palsy is generally very good. The extent of nerve damage determines the extent of recovery. Improvement is gradual, and recovery times vary.

Burning mouth syndrome

(Synonyms: Glossodynia; glossopyrosis; stomatopyrosis)

Burning mouth syndrome (BMS) is a painful condition characterized by burning sensation in the tongue, lips, palate, or throughout the mouth.

Pathogenesis

It often occurs with a range of medical and dental conditions, from nutritional deficiencies and menopause to dry mouth and allergies, but the exact cause cannot be always identified with certainty.

- Damage to inferior alveolar nerve or chorda tympani nerves
- Hormonal changes
- Xerostomia
- Nutritional deficiencies
- Oral candidiasis
- Poorly fitting dentures or allergies to denture materials
- Anxiety and depression

Clinical features

- **Age.** Older age group.
- **Sex.** Female predilection.
- **Signs and symptoms**

- Moderate to severe burning in the mouth is the main symptom of BMS and can persist for months or years. For many people, the burning sensation begins in late morning, builds to a peak by evening, and often subsides at night.
- Pain may be consistent or intermittent.
- Glossodynia (painful tongue) and glossopyrosis (burning tongue).
- Tingling or numbness on the tip of the tongue or in the mouth.
- Bitter or metallic changes in taste.
- Dry or sore mouth.

Prognosis and predictive factors

Depending on the cause and symptoms, possible treatments include:

- Adjusting or replacing irritating dentures.
- Treating existing disorders such as diabetes, Sjögren's syndrome or a thyroid problem to improve burning mouth symptoms.
- Supplements for nutritional deficiencies.
- Prescribing medications to:
 - Relieve dry mouth.
 - Treat oral candidiasis.
 - Help control pain from nerve damage.
 - Relieve anxiety and depression.
- When no underlying cause can be found, treatment is aimed at the symptoms to try to reduce the pain associated with BMS.

Auriculotemporal syndrome

(Synonyms: Frey's syndrome; Frey–Baillarger syndrome; gustatory sweating syndrome)

- It was first described by Duphenix in 1757 in association with parotid gland trauma, then Lucja Frey in 1923 correlated the previously described findings to the distribution of the auriculotemporal nerve and coined the term *auriculotemporal syndrome.*
- This term is misleading, as the skin innervated by the greater auricular nerve, the lesser occipital nerve the long buccal nerve, or any cutaneous branch of the cervical plexus may be involved.
- *Frey's syndrome (FS)* is the phenomenon secondary to gustatory stimulus, manifested by flushing and sweating in the preauricular region consequent to injury of auriculotemporal nerve.

Pathogenesis

- The injury to the auriculotemporal nerve may be from any of the following causes:
 - Penetrating wound of the parotid region
 - Infection of the parotid region
 - Parotidectomy
 - Birth trauma—trauma of the auriculotemporal nerve after forceps delivery
 - Mandibular and zygomatic fractures
 - Temporomandibular joint (TMJ) surgery
 - Internal maxillary artery pseudoaneurysm
 - Diabetes mellitus
 - Herpes zoster
 - Platinum-induced neuropathy
 - CNS diseases (syringomyelia, cerebrovascular accident, encephalitis)
- The auriculotemporal branch of the trigeminal nerve carries sympathetic fibres to the subcutaneous sweat glands and parasympathetic fibres to the parotid gland.
- FS is believed to be the result of misdirected autonomic nerve regeneration following injury to the parotid region. After injury, the sectioned postganglionic secretomotor parasympathetic fibres which normally innervate the parotid gland regenerate and get misdirected and connected to sympathetic receptors, which innervate sweat glands and subcutaneous blood capillaries. Hence, stimuli that normally cause salivation (smell, sight and thought of food) simultaneously cause pathologic vasodilatation, sweating and flushing in the preauricular area on the side of the nerve injury (Fig. 19.1).
- *Crocodile tears:* Similar injury to nerve fibres, during submandibular gland surgeries, results in excessive tear formation in response to gustatory stimuli. This is called gustatory lacrimation.

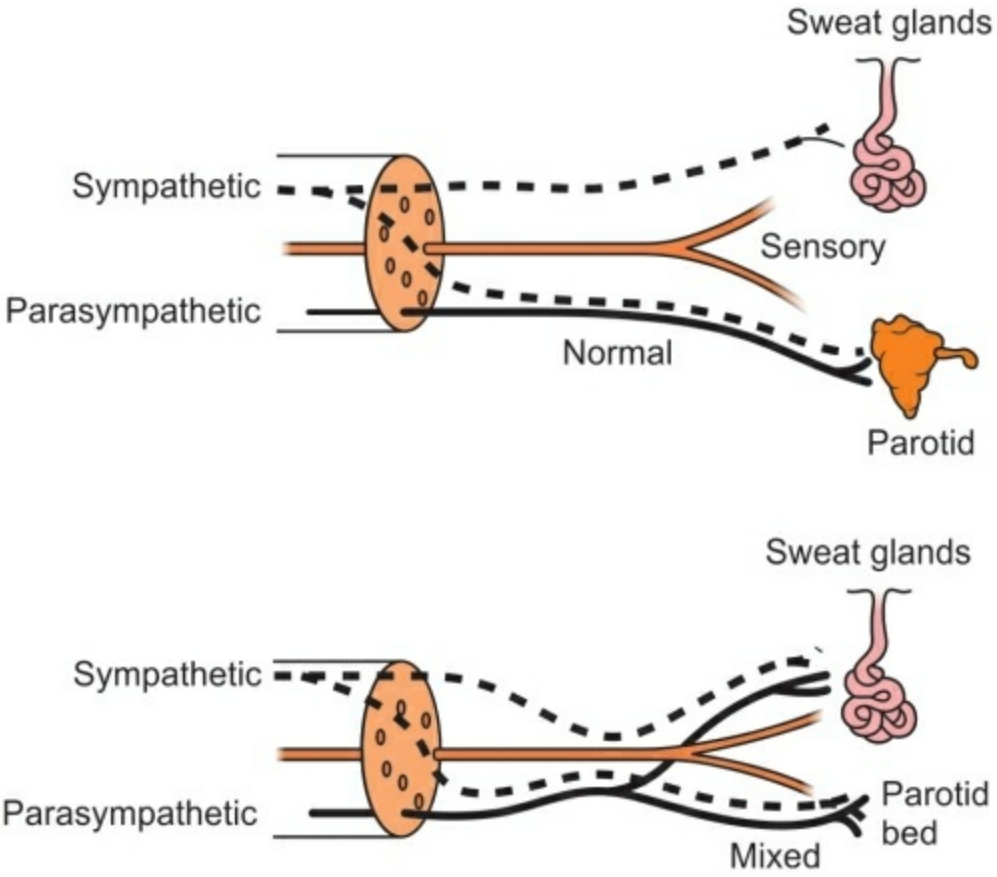


FIG. 19.1 Proposed mechanisms of Frey's syndrome.

Clinical features

- Severity of symptoms varies from person to person. Few of them may have slight localized increase of temperature and erythema of preauricular skin with gustatory stimuli, whereas some suffer from profuse sweating and facial flushing.
- Although FS does not cause significant physiological harm, profuse gustatory flushing and sweating can cause social embarrassment and psychological distress in some patients.

Diagnosis

- FS is diagnosed by history and clinical examination and can be confirmed with the minor starch-iodine test.
- **Minor starch-iodine test:** Paint the affected side of the face with iodine and let it dry. The area is subsequently powdered with corn-starch. To elicit salivation or sweating, the patient is asked to chew a lemon slice for 5 minutes. The appearance of black spots over the starched field

constitutes a positive result, generated by a chemical reaction between iodine, dissolved starch and sweat, confirming sweating secondary to gustation. The margins of the black spots are drawn with a ball-point pen. The black spots can be used to pinpoint where to use the Botox and give a semiquantitative recording of how the gustatory sweating is improving (or not). However, the minor starch-iodine test has few drawbacks:

- It is difficult to use in hair-bearing areas of the skin.
- It does not allow evaluation of the severity of the gustatory sweating.

Prognosis and predictive factors

- In most cases, FS patients do not complain of their symptoms and are often treated effectively with topical antiperspirant gels applied to the affected area.
- However, when the symptoms become annoying, various prophylactic and therapeutic surgical strategies have been proposed to minimize the incidence or severity of FS following parotidectomy.

Orolingual paraesthesia

Orolingual paraesthesia includes altered sensation of oral mucosa membrane due to any insult to the nerve.

Pathogenesis

Any injury or damage to lingual nerve and inferior alveolar nerve can result in anaesthesia (numbness), paraesthesia (tingling) or dysaesthesia (pain and burning) in the tongue, lips, chin and lower jaw.

Clinical features

- Damage to the lingual nerve results in pain within the tongue and inner buccal mucosa.
- The patients suffer from burning or dull or achy pain or numbness could be the only symptom.
- In general, the inferior alveolar nerve injuries (mucosa and lip numbness) are tolerated well than the lingual nerve injuries (affect tongue and inner gingival mucosa).

Prognosis and predictive factors

- Most of the injuries resolve on their own.
- Short course of corticosteroids, if the injury is recent.
- Palliative treatment for nerve pain—topical lidocaine, capsaicin candies, systemic analgesics, acupuncture, nerve block and neurectomy in severe cases.

Atypical facial pain

The term *atypical facial pain (AFP)* is used to describe the facial pain for which no cause can be found and which does not respond to the usual analgesics.

Pathogenesis

The exact aetiology is still unknown and many possible causes are proposed:

- Some studies postulate a low-grade infectious and inflammatory process occurring over a long period can result in nerve damage and could be the triggering factor for AFP pain.
- Some believe that vascular compression of the trigeminal nerve in the same area that is postulated to lead to trigeminal neuralgia is a cause of AFP.
- Dental or some sort of physical trauma is also linked to AFP.

Clinical features

- **Age.** Older age group.
- **Sex.** Female predilection.
- **Signs and symptoms**
 - The pain can be intermittent or continuous of varying intensity and can last for years.
 - It may affect a small area of the face, but it can also spread across the whole of the face and mouth.
 - The pain is described as nagging, throbbing, burning, pinching, pulling, aching and is unilateral, often in the region of the trigeminal nerve and can extend up to the upper neck or back of the scalp.
 - **Clinical presentation**

Symptoms

- Site
 - Pain in the region of the ear may be referred from the skin, teeth, tonsils, pharynx, larynx or neck.

 - Tenderness over the maxilla may be due to sinusitis, dental abscess or carcinoma.
 - *Character*
 - Trigeminal neuralgia: Intermittent sharp, severe pain in the distribution of the divisions of the trigeminal nerve.
 - Infections of teeth, mastoid and ear: Often dull, aching quality.
- Precipitating factors
 - Precipitated by food or chewing: Dental abscess, salivary gland disorder, TMJ disorder or jaw claudication due to temporal arteritis.
 - Trigeminal neuralgia: Even slightest touch of the skin causes intense pain.
- Associated symptoms
 - Obstruction of the lacrimal duct by nasopharyngeal carcinoma may cause watering of the eyes.
 - Otorrhea and/or hearing loss suggest an ear or mastoid cause.
 - Nasal obstruction and rhinorrhoea may be due to maxillary sinusitis or carcinoma of the maxillary antrum. Carcinoma of the maxillary antrum may also present with unilateral epistaxis.
 - Proximal muscle weakness and pain may be due to polymyalgia rheumatica, associated with temporal arteritis.

Signs

- Unilateral erythema and vesicles in the distribution of the trigeminal nerve: Herpes zoster infection.
- Localized erythema or swelling: Localized infection or carcinoma.
- Inspection of nose and throat may demonstrate a nasopharyngeal tumour.
- Facial palsy: May be due to a tumour of the parotid gland.
- Tenderness of the superficial temporal artery associated with temporal arteritis.
- Cervical lymphadenopathy: Infection or carcinoma.

Diagnosis

- A diagnosis of AFP is usually a process of elimination. There are no tests to aid in the diagnosis of this condition.
- For appropriate diagnosis of AFP, the dentist must have a thorough knowledge of the long list of possible causes of facial pain and their clinical presentations. The common causes are:
 - *Sinus:* Sinusitis, trauma, carcinoma
 - *Nose:* Upper respiratory tract infection, nasal injury and foreign bodies

- *Ear:* Otitis media, otitis externa
- *Mastoid:* Mastoiditis
- *Teeth:* Pain of pulpal and periapical pathology
- *Neurological:* Trigeminal neuralgia, herpes zoster
- *Parotid gland:* Mumps, other causes of parotitis, abscess, duct obstruction, calculi, tumour
- *Eye:* Orbital cellulitis, glaucoma
- TMJ dysfunction and pain
- Cluster headaches, migraine
- Temporal arteritis
- *Tumours:* Nasopharyngeal, oral, posterior fossa
- *Bone:* Maxillary or mandibular osteitis, osteomyelitis

- The following tests are helpful in identifying the common causes of facial pain:
 - *Full blood count:* Raised WBC count in infection or malignancy.
 - *ESR, CRP:* Increase in infection, malignancy, temporal arteritis.
 - *X-rays*
 - Opacification of the sinus and destruction of bone with carcinoma of sinuses.
 - Opacification may also occur in sinusitis.
 - Mastoid films may show opacification in cases of mastoiditis.
 - CT or MRI scan: Carcinoma sinuses, nasopharyngeal carcinoma, parotid conditions. Extent of tumours and invasion.
 - *Sialography:* Parotid conditions, e.g. duct stones, sialectasis.
 - *Fine needle aspiration:* Parotid tumours.

Prognosis and predictive factors

Treatment of AFP can be difficult and perplexing for both doctor and patient. Medication is usually the first course of treatment. Surgical procedures such as microvascular decompression generally are not successful with AFP patients. The following drugs are used to treat AFP:

- Amitriptyline
- Gabapentin
- Capsaicin
- Other pain relief strategies include:
 - Hot and cold compresses
 - Acupuncture
 - Dental splint

Diseases of muscle

Muscular dystrophy

- Muscular dystrophy (MD) refers to a group of more than 30 genetic diseases that cause progressive weakness and degeneration of skeletal muscles used during voluntary movement. The word *dystrophy* is derived from the Greek word *dys*, which means *difficult* or *faulty* and *troph* means *nourish*.
- These disorders vary in age of onset, severity and pattern of affected muscles. All forms of MD grow worse as muscles progressively degenerate and weaken. Many patients eventually lose the ability to walk.
- ***Oral manifestations***
 - In cases of mild MD, inability to close the eyes, facial muscle weakness, weak lips, inability to whistle or smile.
 - In cases of severe MD, the muscles of mastication are affected along with all other groups of muscles. The teeth are not properly aligned in the arch due to lack of muscle tension.

Histopathology

There is gradual disappearance of muscle fibres as the disease progresses.

Prognosis and predictive factors

The prognosis varies according to the type of MD and the speed of progression. Some types are mild and progress very slowly, allowing normal life expectancy, while others are more severe and result in functional disability and loss of ambulation. Life expectancy may depend on the degree of muscle weakness and any respiratory and cardiac complications.

Myotonias

- Myotonias are a group of neuromuscular disorders characterized by slow relaxation of muscles after voluntary contraction.
- Repeated effort is needed to relax the muscles, and the condition improves after the muscles have warmed up.
- However, prolonged, rigorous exercise may also trigger the condition. Individuals with the disorder may have trouble releasing their grip on

objects or may have difficulty rising from a sitting position and a stiff, awkward gait.

- Myotonia can affect all muscle groups; however, the pattern of affected muscles can vary depending on the specific disorder involved.
- Patients suffering from disorders involving myotonia can have a life-threatening reaction to certain anaesthetics; one of these conditions occurs when the patient is under anaesthesia and is termed *malignant hyperthermia*.
- Myotonia is not always a disease-related phenomenon. Humans often display myotonia, when placed in situations of extreme stress or fear; a resultant increase in 'fight-or-flight' hormones such as epinephrine and cortisol may cause increased muscle tension throughout the body.

Pathogenesis

- It may be acquired or inherited, and is caused by an abnormality in the muscle membrane—specifically, the ion channels that control the contraction of muscle fibres.
- Myosin is defective in myotonia.

Clinical features

- The main types of myotonias are dystrophic, acquired and congenital.
- Dystrophic myotonia can be encountered by the dentist and is characterized by ptosis of eyelids, atrophy of masseter and sternocleidomastoid muscles.
- Lower part of the face becomes narrow due to muscular weakness and atrophy and is referred to as *myopathic face* and *swan neck*.

Prognosis and predictive factors

There is no treatment, the disease progresses causing disability and ultimately death.

Myositis/myositis ossificans

Myositis refers to inflammation of muscle tissue and could be caused by physical and chemical injuries to the muscles as well as infections. Of all the forms of myositis, traumatic myositis ossificans of the masticatory muscles and dermatomyositis are frequently encountered by the dentist.

Myositis ossificans

- The term *myositis ossificans* refers to the formation of bone within a muscle. It is a disorder of unknown cause in which connective tissue and muscle are replaced by bone.
- It is of two types:
 - In the more common 'local type' (myositis ossificans circumscripta), only one area is affected and ossification occurs in a muscle following injury. This condition is also known as *traumatic myositis ossificans*. It needs immediate treatment and has a good prognosis.
 - The rare 'progressive type' (myositis ossificans progressiva) is characterized by ossifications in muscles and connective tissue fascia without any injury, group after group of muscles become ossified in a predictable manner, until the individual is completely rigid. This is known as *Stiffman syndrome* and is inherited in an autosomal dominant pattern. Breathing and swallowing become difficult, and fatal respiratory infections may occur. The survival rate is usually low and the use of medications to prevent calcification may slow the progression of the disorder.

Oral manifestations

- Traumatic myositis ossificans (TMO) can affect the muscles of mastication.
- Masseter is commonly affected followed by temporalis, medial and lateral pterygoid muscles.
- The patients complain of difficult in opening the jaws and usually give a history of trauma.
- The condition is benign and results in reactive heterotopic bone formation.
- The specific cause and pathophysiology are unclear—it may be caused by an interaction between local factors (e.g. a reserve of available calcium in adjacent skeletal tissue, soft tissue oedema, vascular stasis tissue hypoxia or mesenchymal cells with osteoblastic activity) and unknown systemic factors. The basic mechanism is the inappropriate differentiation of fibroblasts into osteoblasts. Early oedema of connective tissue proceeds to tissue with foci of calcification and then to maturation of calcification and ossification.

Radiographic features

The typical radiographic appearance of myositis ossificans is circumferential calcification with a lucent centre, and a radiolucent cleft that separates the lesion from the cortex of the adjacent bone.

Histopathology

- Myositis ossificans is essentially extraosseous bone formation (without inflammation) which occurs in muscle.
- It has a zonal organization:
 - Peripheral well-organized mature lamellar bone
 - Intermediate osteoid region
 - Central immature non-ossified cellular focus
- Unfortunately, the histology of myositis ossificans can appear reminiscent of osteosarcoma, and thus can actually lead to inappropriate management.

Prognosis and predictive factors

Immobilization, anti-inflammatory drugs, physiotherapy and early surgical intervention with wide excisional biopsy of the lesion is done.

Myasthenia gravis

- Myasthenia gravis (MG) is a chronic neuromuscular disease characterized by fluctuating muscle weakness and fatigability.
- It is an autoimmune disease caused by circulating antibodies that commonly act against the nicotinic acetylcholine receptor (nAChR); the receptor in the motor end plate for the neurotransmitter acetylcholine that stimulates muscular contractions.
- The hallmark of MG is fatigability. Muscles become progressively weaker during periods of activity and improve after periods of rest. Muscles that control eye and eyelid movement, facial expressions, chewing, talking and swallowing are especially susceptible.
- The degree of muscle weakness involved in MG varies greatly among patients, ranging from a localized form that is limited to eye muscles, to a severe and generalized form in which many muscles are affected.

Dental considerations

- The facial muscles are commonly involved, giving the patient an immobile

and expressionless appearance. Patients with MG cannot wear complete dentures because of the weak muscles; they have a hard time chewing their food, keeping their mouths closed; when they eat, have a weakened tongue and a weakened palate.

- This disease commonly affects middle-aged females and the patients often exhibit difficulty in mastication, deglutition, dropping of jaw, slurred speech and loss of taste sensation.
- Dental management of patients diagnosed with MG presents a challenge to the dental profession. Multiple, short early morning appointments should be scheduled and oral anticholinesterase agents should be administered 1 hour before dental treatment to achieve maximal effect during the dental procedures.

Treatment

- Medical: Immunosuppressive drugs in combination with cholinesterase inhibitors.
- Surgical: Thymectomy.

Muscular hypertrophy

Increase in the size of individual muscle fibres results in hypertrophy of the muscle. It should be differentiated from pseudohypertrophy where muscles increase in size owing to overall increase in the size of interstitial connective tissue.

Aetiology

- Developmental defects
- Inflammation
- Functional disturbances
- Neoplasm
- Metabolic disturbances
- The commonly occurring muscular hypertrophies are macroglossia and masseter hypertrophy.
 - Macroglossia is discussed in detail in Chapter 1 Developmental Disturbances of Oral and Paraoral Structures.
 - Masseter hypertrophy could be congenital or acquired. When acquired, it could be a functional hypertrophy due to over usage owing to a habit or due to surgical procedures.

Key points

- *Trigeminal neuralgia* means pain along the distribution of trigeminal nerve. It is a sudden, sharp, lancinating, electric shock-like recurrent pain in the distribution of one or more branches of the trigeminal nerve.
- *Bell's palsy:* Dropping of angle of mouth on affected side, inability to raise eyebrow on affected side, inability to close eye on affected side, excessive tearing or dry eye, Bell's phenomenon and expressionless face.
- *Frey's syndrome* is the phenomenon secondary to gustatory stimulus, manifested by flushing and sweating in the preauricular region consequent to injury of auriculotemporal nerve.
- *Atypical facial pain* is a facial pain which does not have any significant cause and does not respond to the usual analgesics.
- *Muscular dystrophy* refers to a group of genetic diseases that cause progressive weakness and degeneration of skeletal muscles used during voluntary movement.
- *Myotonias* are a group of neuromuscular disorders characterized by slow relaxation of muscles after voluntary contraction.
- *Myositis* refers to inflammation of muscle tissues and could be caused by physical and chemical injuries to the muscles as well as infections.
- *Myasthenia gravis* is a chronic neuromuscular disease characterized by fluctuating muscle weakness and fatigueability.

Frequently asked questions

1. Trigeminal neuralgia
2. Facial paralysis or Bell's palsy
3. Burning mouth syndrome
4. Frey's syndrome
5. Myositis ossificans
6. Myasthenia gravis

CHAPTER 20

Forensic odontology

Forensic dentistry

A branch of dentistry which, in the interest of justice, deals with the proper handling and examination of dental evidence and with the proper evaluation and presentation of dental findings (FDI).

Or

The branch of dentistry that deals with the legal aspects of professional dental practice and treatment, with particular emphasis on the use of dental records to identify victims of crimes or accidents (*Mosby's Medical Dictionary*).

Or

In simple words, it is the application of dentistry to the judicial system.

Role of a forensic odontologist

Forensic odontologist, a dentist, is one who is trained to identify, document, preserve the collected evidences from a crime scene and disaster, and finally present the same in the court of law. These data or evidences are normally collected by the investigators or evidence technicians, which are then transported to the forensic odontologist for further analysis.

From crime scene, disaster and archeological sites, these data are sent to a forensic odontologist to:

- Identify remains of individual.
- Determine gender and age of the individual.
- Evaluate bite marks, lip prints, palatal rugae or tooth enamel patterns for identification of the individual.

Personal identification

Identification of an individual or person is one foremost important step in the field of forensic sciences. Forensic odontology helps in personal identification by the use of pre-mortem and post-mortem dental identification.

Pre-mortem dental identification

- Dental and surrounding tissue details or changes:

 - Dental casts
 - Dental radiographs
 - Photographs of individuals
- Charting the details

Antemortem dental identification

Dental and surrounding tissue details or changes charted.

Comparison of post-mortem and antemortem details

- In forensic cases, the process of using photographs, radiographs and charting details can be an accurate and efficient method for making a positive identification or exclusion of individuals.
- In a forensic odontology scenario for identification of an individual, the initial goal of the forensic dentist is in obtaining postmortem photographs, radiographs and accurate dental charting (from impressions, casts, dental radiographs) on the unidentified person. Collecting the antemortem details could also be difficult, on obtaining an insight into the details of the unidentified individual from the post-mortem details; antemortem details can be easily collected.
- The dental details can be obtained from the dentists or dental facilities in the form of dental charting of the teeth, financial records for treatment rendered, photographs and radiographs that would be part of a dental examination are important items to collect as part of the antemortem reconstruction. The detailed reconstruction of the dental records and the comparison of these details results in positive identifications of the individual.

Palatal rugae for personal identification

(Synonym: Plicapalatinae)

Palatal rugae are defined as anatomical folds or wrinkles; the irregular fibrous connective tissue located on the anterior third of the palate behind the incisive papilla.

Characteristic features of rugae

- Asymmetrical in nature.
- Irregular elevated folds of mucosa.

- These are arranged in transverse direction.

The palatal rugae seem to help in various functions such as speech, taste, swallowing. In forensic odontology, they seem to help in medicolegal identification.

The advantage of palatal rugae is that as a result of internal positioning, they are protected in burn victims and not costly to reproduce or record.

Classification

It is based on the number, shape and length of the rugae:

- Number—if the rugae are united, diverged or converged.
- Shape—they are divided into curved, wavy, straight and circular shapes.
- Length—they are divided into primary, secondary and fragmented rugae:
 - Primary rugae are of 10 mm and more in length.
 - Secondary rugae are of 5–10 mm in length.
 - Fragmented rugae are less than 5 mm in length.

The classified rugae can be compared between the post-mortem and the antemortem records (impression or casts). The tracing paper can be adapted to the casts and can be traced out. Thus, identity of the individual can be established.

Lip prints for personal identification

(Synonym: Cheiloscopy)

The wrinkles and grooves on the labial mucosa, called as *sulci labiorum,* form a characteristic pattern called *lip prints*. The study of lip prints is known as *cheiloscopy*. Lip prints are unique to an individual like fingerprints. Latent lip prints (without lipstick) are produced due to sebaceous and saliva on the vermilion border.

Methods of recording lip prints

- Coloured lipstick is applied on the lips and the subject is asked to spread it uniformly over the lips.
- Over the lipstick, the glued portion of the cellophane tape is dabbed first in the centre and then pressed uniformly over the corner of the lips.
- Lip prints are traced in the normal rest position of the lips. The cellophane tape is stuck to the white sheet for permanent recording.

Classification

Suzuki and Tsuchihashi system for classifying lip prints is as follows:
1. Type I—a clear-cut groove running vertically across the lip
2. Type II—partial length groove of type I
3. Type III—a branched groove
4. Type IV—an intersected groove
5. Type V—a reticular pattern
6. Type VI—other patterns

Applications

- Among the soft tissue structures, lip prints can be recorded and used as evidence in personal identification and criminal investigation.
- In criminal investigations, criminals during robbery, murder, sexual harassment and rape may use certain materials with lips like drinking glass or cigarette, and the lip print would be fixed.
- If the lip print is identified from the material during investigation, this recorded lip print can be compared with the lip prints from suspected persons. If the lip print from the glass matches with a particular suspected person's lip print, then that person is considered as the culprit.
- The major disadvantage of lip print investigation pertains to doubts about the permanence of lip patterns.

Bite marks for personal identification

Bite marks are defined as distinctive tooth patterns in a wound that may have forensic or legal implications.

Collection and recording of data

- Identification of whether maxillary or mandibular teeth
- Individual teeth characteristic
- Specific teeth characteristic

Evidence from a potential biter would include dental examination, photographs, dental impressions and casts. In addition to the above physical methods, saliva could act as a source for molecular analysis.

Analysis of data

- The bite mark can vary based on certain parameters like the force and duration of bite, site of the body where the bite had occurred. The bite

marks on living tissue change with time.

- It includes the comparison of the bite mark with the dental evidence:
 - Direct comparison
 - Indirect methods: Tracing the marks or using computer generated images

Reporting bite mark evidence

- Reasonable dental/medical certainty
- Probable
- Inconclusive

Ameloglyphics

Odontogenesis is genetically modulated. The formation of enamel is a highly organized dynamic process, in which the ameloblasts lay down the enamel rods in an undulating and intertwining path. This is reflected on the outer surface of the enamel as a series of enamel rod end patterns. The term *ameloglyphics* means *the study of enamel rod end patterns* (*amelo* means *enamel*; *glyphics* means *carvings*).

Procedure

Procedures of ameloglyphics are shown in Figures 20.1–20.4.



FIG. 20.1 Condition the tooth surface using 10% orthophosphoric acid.

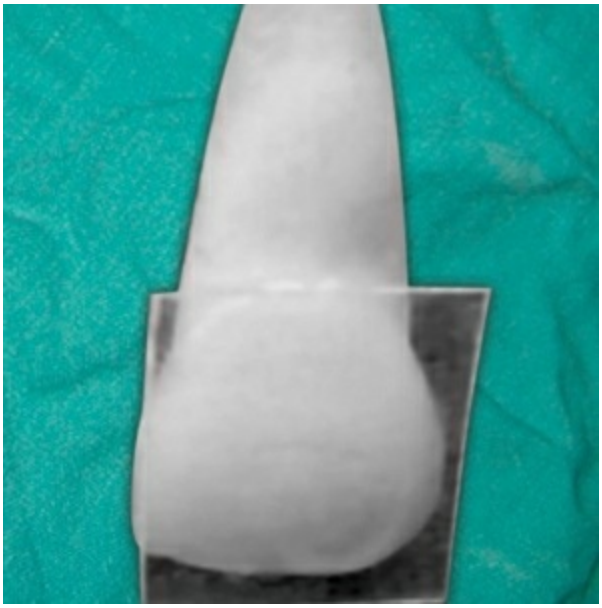


FIG. 20.2 Cellulose acetate film with thin layer of acetone placed over conditioned surface for 20 minutes.



FIG. 20.3 Microphotograph of enamel rod endings on tooth surface at 40× magnification.

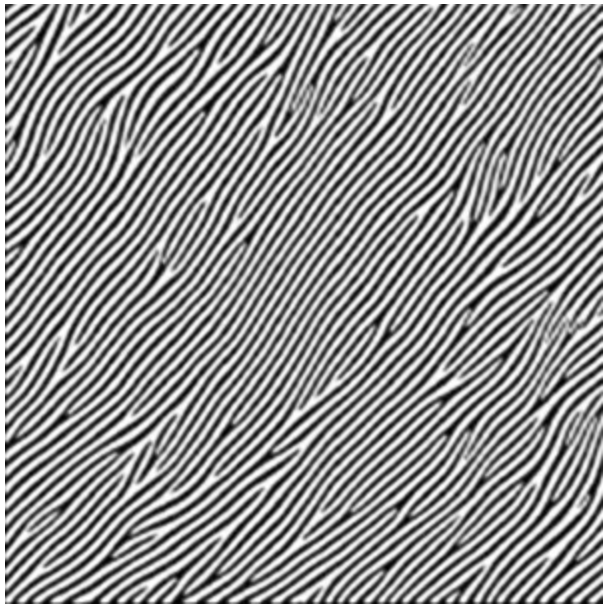


FIG. 20.4 Enamel rod end pattern obtained using biometric software with combination of distinct subpatterns.

Significance

Figure 20.5 shows eight distinct subpatterns observed in enamel rod end pattern.

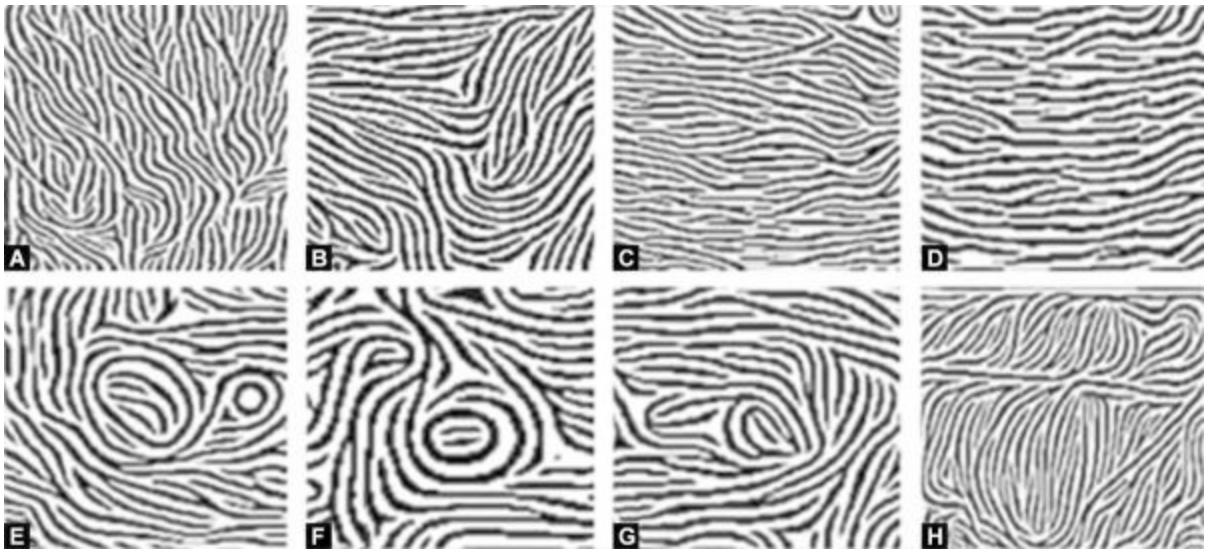


FIG. 20.5 Eight distinct subpatterns are observed in enamel rod end pattern. (a) Wavy branched, (b) wavy unbranched, (c) linear branched, (d) linear unbranched, (e) whorl open, (f) whorl closed, (g) loop, (h) stem-like.

Enamel is the hardest substance in our body, which can withstand very high temperature. Enamel rod end patterns are unique to a single tooth and exhibit dissimilarity both between teeth of different individuals and of the same individual. Ameloglyphics is a highly reliable biometric-based procedure for personal identification. This technique is simple, inexpensive and rapid, and can also be performed by nonprofessionals. This uniqueness of the ameloglyphics could be used as a valuable tool, which could be incorporated with other techniques like fingerprint, face identification, iris scanning, etc. for regular personal identification. On a regular basis it is recommended for individuals working in dangerous occupations such as fire fighters, soldiers, jet pilots, divers and people who live or travel to politically unstable areas prior to their assignments. It has a greater role in personal identification especially in mass disasters where soft tissue mutilation fails to provide reliable information.

Forensic genetics

(Synonym: DNA fingerprinting)

Human identification is one of the major fields of study and research in forensic science because it deals with the human body and aims at establishing human identity.

Source of genetic material

Genetic material can be isolated from virtually all human body tissues but a variation in the quantity and quality is evident. Commonly used sources are:

- Saliva
- Blood
- Semen or vaginal secretions
- Hair bulb or follicle
- Bony tissue
- Tooth
- Biopsy tissue from a lab

Analysis of genetic material

- There are repeated sequences spread throughout the human genome and present sufficient variety to be used in human identification tests. These hypervariable loci (location in genome) are constituted by tandem repeat of oligonucleotides sequences (from 2 to 80 bp). Based on the size of locus, three polymorphic or repeat sequences are used:
 1. Variable number of tandem repeat (VNTR) or mini satellites of 9–80 bp (base pair) size
 2. STR (short tandem repeats) or microsatellites of 2–5 bp (base pair) in size
 3. SNP (single nucleotide polymorphism) of only one nucleotide sequence
- In earlier times, the forensic community used VNTR testing for body identification and paternity tests. However, as this method requires a large amount of material, it has low quality results.
- STR testings were started to be used for forensic casework after the introduction of techniques which increase or amplify the minimum quantity of DNA by PCR technique, making a revolution on human identification and paternity tests. Nowadays, SNPs are used in forensic identification.

Application of tooth in forensic genetic

- The crown of teeth is covered by the hardest substance in the body, i.e. enamel and root are embedded in the bone. The living tissues of tooth and jaws are normally protected from extremes of temperature or environmental conditions and can act as a good source of genetic material.

- Quantity and quality of DNA from dental tissues can be obtained from pulp, followed by cementum and dentine.
- DNA quality depends on various factors like the environmental factors, type of DNA extraction and decalcifying agent procedures.

- DNA isolation from teeth, in cases of human remains in which a victim's body is almost completely carbonized (burnt), can be subjected to DNA analysis by the usual methods. DNA from tooth can be used to determine gender by genes *amelogenin* and *SRY*.

Age estimation in forensic odontology

- The dentist and forensic odontologist can estimate the age of the deceased, help reconstruct the person's dental profile and compare these data of potential identities using dental comparison techniques. The presence or absence of teeth can help in estimating the age. The morphological features like attrition, colour of dentition can help to identify age of the individual.
- Tissue changes occur with chronological age. Bones act as a good informer about growth and growth changes. Hard tissue development in bones, cranial sutures and teeth take place at specific ages. They are affected by genetics, general health and other environmental factors.
- Dental hard tissues and bones are extremely resistant to fire and are usually the only remains after an extended period of burial. Age estimation, an important parameter in establishing the identity, can be done by hard tissue examination; it becomes tough with the maturity of individual. Therefore, age determination is divided into two phases:
 1. Phase I—formative till 12 years of age
 2. Phase II—degenerative after 12 years of age
- Clinically evident—attrition of tooth and periodontitis.
- Radiographic—size of pulp chamber or presence/absence and level of tooth or degree of formation of crown and root in panoramic radiograph could act as predictive factors.
- Microscopically evident—secondary dentine formation, cementum deposition in annual pattern and root dentine transparency.
- Biochemical increase in D-aspartic acid levels with age, in dental hard tissue.

Sex determination in forensic odontology

In a decomposed body, the gender or sex determination is commonly done by size and shape of the hard tissue structures, bones and teeth. In addition to these analytical techniques, DNA can also act as a source of gender determinant. Sexual dimorphism means the differences in sex, stature and appearance between different sexes in the same species.

- **Teeth:** Mandibular canine index and width
- **Bone:** Features of bones are:
 - Head and neck
 - Pelvic bone
- **DNA:** Genes commonly used are:
 - Amelogenin gene
 - SRY gene

Mandibular canine in sex/gender determination

- Among all the above listed features of dimorphism, the mandibular canine index is the most favourable feature. The teeth can normally withstand severe changes in temperature and also exhibit a high amount of dimorphism. The mean values of the buccolingual and mesiodistal dimensions of the mandibular left canine are greater in females than in males.
- The methods commonly employed to check the dimorphism include:
 - Dimensions of the canine (mesiodistal and buccolingual)
 - Canine index
- Canine index is calculated by dividing the mesiodistal width of the canine by the intercanine width.
- **Formula**

$$\text{Mandibular canine index} = \frac{\text{Mesiodistal width of mandibular canine}}{\text{Mandibular canine arch width or intercanine distance}}$$

- The mandibular canine index of less than 0.28 is mostly a female individual.

Bone in sex determination

- **Features in head and neck**
 - The cranium of males is more bulky and prominent.

- Forehead of the male extends more downwards on to the face.
- In males, the supraorbital ridge is more rounded.
- Zygomatic bone and mandible are more prominent in males (square-shaped in males).
- The angle of the mandible (gonion) is more pointed in males.

- **Features on pelvic bone**
 - Pelvic bone is wider in females than in males.
 - Preauricular sulcus of the pelvis is more prominent in women.
 - Sciatic notches and pubic arch are wider in females.

DNA in sex determination

Molecular methods in sex or gender determination are commonly helpful in fragmented remains or skeletal remains of young.

- *Amelogenin:* It is the commonly used gene for sex determination. This gene leads to false female sex identification or labelling with mutations in primer binding areas of the Y homologue sequence of amelogenin gene.
- *SRY* gene: On the Y chromosome, it is used in STR for identification of gender of the individual (male).

Key points

- *Forensic odontology* is a branch of dentistry which in the interest of justice deals with the proper handling and examination of dental evidence and with the proper evaluation and presentation of dental findings.
- *Palatal rugae analysis*: Based on the number (united, diverged or converged), shape (curved, wavy, straight and circular shapes) and length (primary, secondary and fragmented rugae) of the rugae.
- *Lip prints analysis: Type I*—a clear-cut groove running vertically across the lip, *Type II*—partial length groove of type I, *Type III*—branched groove, *Type IV*—intersected groove, *Type V*—reticular pattern and *Type VI*—other patterns.
- *Bite marks* are defined as distinctive tooth patterns in a wound that may have forensic or legal implications.
- *Ameloglyphics* means the study of enamel rod end patterns.
- *Ameloglyphic subpatterns:* Wavy branched, wavy unbranched, linear branched, linear unbranched, whorl open, whorl closed, loop and stem-like subpatterns.
- *Genetic analysis:* Based on number of tandem repeat or mini satellites of 9–

80 bp size, STR (short tandem repeats) or microsatellites of 2–5 bp in size and SNP (single nucleotide polymorphism) of only one nucleotide sequence.

- *Age determination:* Clinical evaluation, radiographs, microscopic evidence of secondary dentine formation, cementum deposition in annual pattern and root dentine transparency and biochemical evaluation of D-aspartic acid levels.
- *Sex determination:* Teeth (mandibular canine index), bone (features of head and neck and pelvic bones) and DNA (*amelogenin* and *SRY* genes).

Frequently asked questions

1. Discuss the application of palatal rugae for identification of individuals.
2. Lip prints for personal individuals.
3. Bite marks for personal identification.
4. Ameloglyphics
5. Discuss about estimation of age and its role in identification of the individual.
6. Discuss about determination of gender or sex and its role in identification of the individual.

CHAPTER 21

Histochemistry

Histochemistry is defined as the study of the chemistry of tissue components by histological methods.

Tissue biopsy

Biopsy is the removal of tissue from the living organism for the purposes of microscopic examination and diagnosis.

Types of biopsy

- Total excision of a small lesion for microscopic study is called *excisional biopsy.* Excisional biopsy is preferred, if the size of the lesion is such that it may be removed along with a margin of normal tissue and the wound can be closed primarily.
- In case of larger lesions, a small piece of tissue is removed for examination. This is termed as *incisional* or *diagnostic biopsy.*

Methods of taking biopsy

- Surgical excision by scalpel
- Surgical removal by cautery or a high frequency cutting knife
- Laser
- Removal by biopsy forceps or biopsy punch
- Aspiration through a large bore needle
- The exfoliative cytology technique

Principles of biopsy

- Before biopsy is undertaken, the patient should be informed about the procedure and reason why it is performed to avoid the anxiety.
- The characteristics of the lesion such as size, shape, colour, texture and consistency should be described in the patient's clinical record with a provisional diagnosis and possible differential diagnosis.
- Regarding the surgical procedure, regional block with local anaesthesia is preferred rather than infiltrative technique.
- Elliptical incision should be attempted to ease suture and healing.
- Incision must be placed parallel to nerves and vessels to prevent the

damage of them.

- The size of the sample should be larger enough to perform the histopathological procedures.
- If the lesion is smaller than 1 cm, excisional biopsy should be performed. In larger lesions, the incisional technique is performed in representative area with adjacent normal tissue.

Fixation of tissue specimens

- The treatment of biological specimens with chemical solutions to preserve the cellular structure so that it is resistant to damage during subsequent processing steps including dehydration, embedding and sectioning.
- The aim of fixation is to preserve tissue in as life-like manner as possible.
- The ideal solution for tissue fixation is 10% formalin (4% formaldehyde).
- The tissue sample should be completely immersed in a fixing solution, preferably the volume of fixing solution should be 10–20 times the size of the sample. The purposes of fixation are to coagulate the protein, thus reducing alteration by subsequent treatment and to make the tissues more readily permeable to the subsequent applications of reagents. The ideal fixation period is 24 hours.

Classification of fixatives

Fixation of tissues can be accomplished as follows:

- **Physical methods:** Heating, microwaving and freeze drying
- **Chemical methods**
 - *Cross-linking fixatives:* Formaldehyde, glutaraldehyde
 - *Coagulation fixatives*
 - Via dehydration of free water: Ethanol, methanol and acetone
 - Via changes in pH or salt formation: Acetic acid, trichloroacetic acid, mercuric chloride, zinc acetate and picric acid
- **Compound fixatives:** Mixture of reagents
 - *Microanatomical fixatives:* Formal calcium, alcoholic formalin, buffered formalin
 - *Cytological fixatives:* Carnoy's fluid, Clarke's fluid, Flemming's fluid, Champy's fluid, Muller's fluid, formal calcium
 - *Histochemical fixatives:* Formal saline, cold acetone, absolute alcohol

Factors affecting the fixation

Buffer and pH

- In strongly acid environment:
 - The primary amine attracts hydrogen ions to become unreactive compound.
 - Carboxyl groups lose their charges—structure of protein is affected.
 - Hydroxyl groups of alcohols including serine and threonine may become less reactive.
 - Formation of reactive hydroxymethyl groups and cross-linking is reduced.
 - Disrupting the tertiary structure of proteins.
- Buffers are used to maintain optimum pH.
- The commonly used buffers are phosphate, cacodylate, bicarbonate and acetate.

Duration of fixation

- The depth (d) reached by fixative is directly proportional to the square root of duration of fixation (t)

$$d = k\sqrt{t}$$

k = Coefficient of diffusibility, which is specific for each fixative
(10% formaldehyde: 0.79, 100% ethanol: 1)

Thus, the time of fixation is approximately equal to the square of the distance the fixative must penetrate.

Size of the specimen

- Gross specimen should not be rest on the bottom of container of fixative. They should be separated from bottom by fixative-soaked paper or cloth allowing penetration of fixative or processing fluids in all directions.
- Gross specimens should be greater than 0.5 cm.
- Proteins inactivate fixatives, especially those in blood or bloody fluids. Blood specimens should, therefore, be washed with saline prior to put into fixative.
- Fixative volume should be at least ten times the volume of specimen for optimal rapid fixation.

Temperature of fixation

- The diffusion of molecules increases with rising temperature due to rapid movement and vibration.
- The rate of penetration of tissue by formaldehyde is faster at higher temperatures.

Concentration of fixatives

Effectiveness and solubility primarily determine the appropriate concentration of fixatives.

Concentrations:

- >10% formalin—increased hardening and shrinkage.
- <70% ethanol—do not remove free water from tissues.

Osmolality of fixatives

- Hypertonic solutions—shrinkage
- Hypotonic solutions—swelling

The ionic composition of fluids should be isotonic as possible to tissues.

Additives

- The addition of electrolytes and nonelectrolytes to fixatives improves the morphology of fixed tissues.
- These additives include calcium chloride, potassium thiocyanate, ammonium sulphate and potassium dihydrogen phosphate.
- Fixatives buffered with electrolytes such as phosphates cause precipitation of salts in some processors.
- The addition of nonelectrolyte substances such as sucrose, dextran and detergent may improve fixation.

Formaldehyde fixation

- 10% neutral buffered formalin (NBF) is commonly used.
- Pure formaldehyde is a vapour that when completely dissolved in water forms a solution containing 37–40% formaldehyde—*formalin.*
- 10% formalin—*formal*—contains 4% weight to volume of formaldehyde.
- In an aqueous solution, formaldehyde forms methyl hydrate, it reacts with several side chains of proteins to form reactive hydroxyl methyl side groups.
- Formaldehyde reacts with nuclear proteins and nucleic acids.

- Formaldehyde reacts with unsaturated lipids but does not interact with carbohydrates.
- Formaldehyde dissolves in unbuffered aqueous solution and forms an acid solution (pH 5–5.5)—*formic acid.*

Note: 5–10% of commercially available formaldehyde is formic acid.

- *Disadvantages of acid formalin:* Formation of brown-black pigments with degraded haemoglobulin—it is not problematic unless the patients have blood abnormality like sickle cell anaemia and malaria.

Glutaraldehyde fixation

- It combines with same reactive groups as does formaldehyde.
- In aqueous solutions, glutaraldehyde polymerizes forming cyclic and oligometric compounds and also oxidized to glutaric acid.
- To aid in stability, it requires storage at 4°C and pH 5.
- Glutaraldehyde has an aldehyde group on both ends of molecule.
- With each reaction, unreacted aldehyde group may introduce into protein and these aldehyde groups can act to further cross-link the protein.
- Cross-linking is irreversible and withstand acids, urea and heat.
- Extensive cross-linking results in better preservation of ultrastructure, but this method of fixation negatively affects immunohistochemical methods and slows penetration by fixative.
- Glutaraldehyde does not react with carbohydrates or lipids unless they contain free amino groups.

Grossing of tissue specimens

- The majority of biopsies are incisional, however, occasionally small lesions may be excised encompassing diagnosis and treatment in one operation.
- If malignancy is suspected, the biopsy should be of sufficient depth and have a surrounding margin to ensure adequate clearance.
- In case the lesion was not completely excised, it should be orientated. This can be achieved by placing a suture at one known margin, e.g. the anterior or superior margin. This would enable the pathologist to confidently indicate the precise location of any residual tumour.

Tissue processing

Careful handling of the tissue, prompt appropriate fixation and tissue processing will enable a confident histological diagnosis to be reached.

1. **Dehydration of the specimen:** After being washed in running water to remove the formalin, the specimen is gradually dehydrated by being passed through a series of increasing percentages of alcohol for hours. The time required for each step of the process depends on the size and density of the specimen. To ensure that the water is replaced by alcohol, two or three changes of absolute alcohol are used. Since alcohol is not miscible with paraffin to which the tissue will be embedded, the specimen is passed from alcohol through two changes of xylene which is miscible with both alcohol and paraffin.
2. **Infiltration of the specimen with paraffin:** After removal of the tissue from xylene, it is placed in a dish of melted embedding paraffin in an oven regulated to about 60°C for couple of hours.
3. **Embedding the specimen:** The tissue will be embedded in the centre of block of paraffin. Attention must be given here to the orientation of the specimen so that it will be cut in the plane desired for examination. The specimen is now ready to be sectioned on a microtome.
4. **Cutting the sections of the specimen:** The wooden cube to which the paraffin block is attached is clamped on a rotary microtome which is adjusted to cut sections of the desired thickness (4–10 μm) and the sharpened microtome knife is clamped into place for sectioning.
5. **Mounting the cut sections on slides:** Suitable lengths of the paraffin ribbon are then mounted on a microscope slide. The preparation of slide is done by the coating of clean slides with a thin film of Meyer's albumin adhesive. A short length of paraffin ribbon is lifted from the water bath and then placed on a constant temperature drying table, which is regulated to about 42°C, so that the sections will adhere to the glass slide. The slide is then allowed to dry on this table. Then it is placed on a constant temperature drying table, which is regulated to about 42°C, so that the sections will adhere to the slide. The slide is then allowed to dry on this table.

Staining

- The objective of staining tissue section is to impart colour and therefore contrast to specific tissue constituents. Though there are various stains

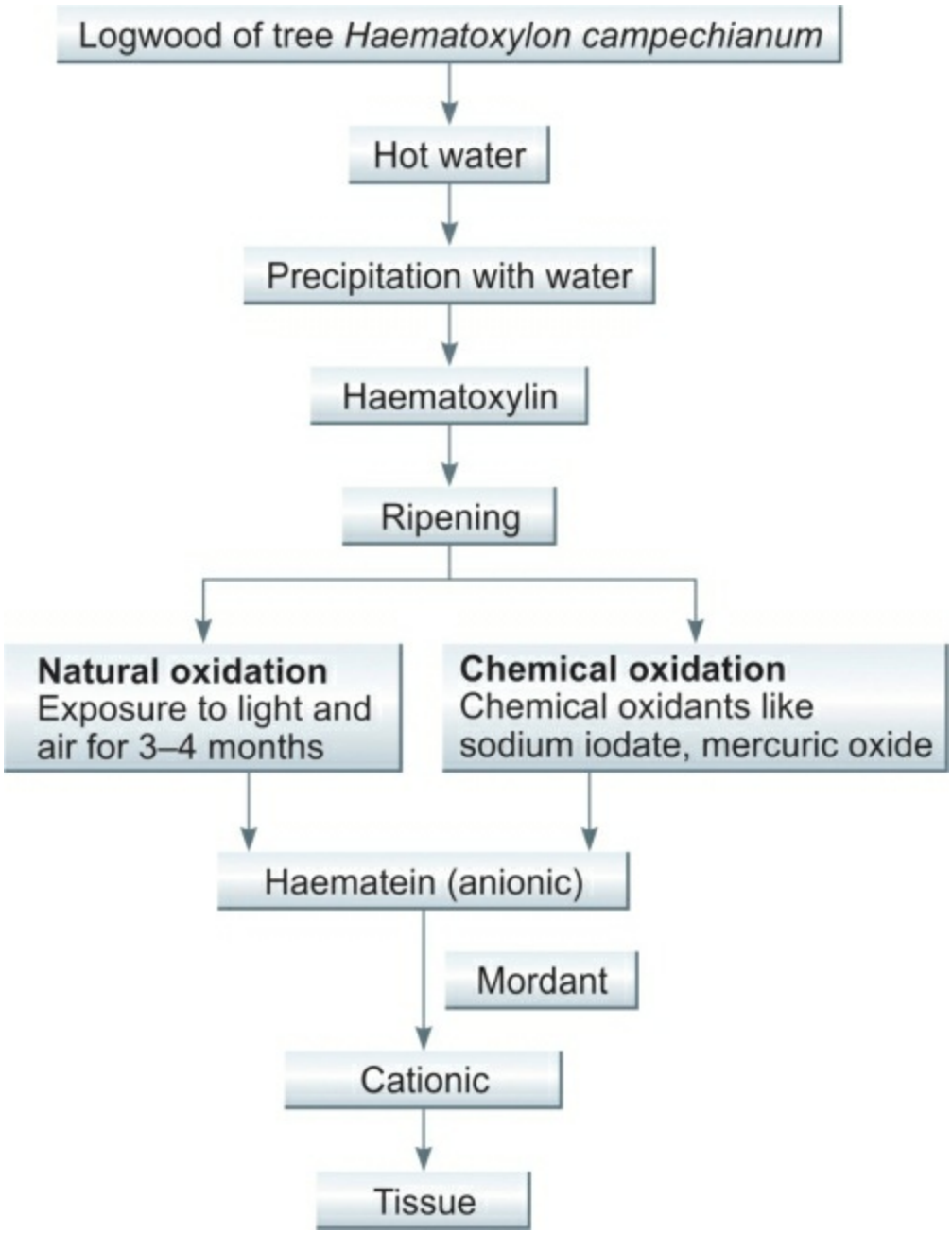
and staining methods, the most commonly used stains in the histological procedures are haematoxylin—nuclear staining and eosin—cytoplasmic staining.

- After staining, the sections are covered with a mounting medium and a cover glass. When the mounting medium has hardened, the slides are ready for microscopic examination.

Haematoxylin and eosin staining (H and E staining)

Haematoxylin

- Haematoxylin is extracted from the logwood of the tree *Haematoxylon campechianum.* The processing of haematoxylin is illustrated in Flowchart 21.1.
- Haematoxylin is not a stain. The major oxidation product is haematein, a natural dye that is responsible for colour properties.
- Haematein is anionic and has poor affinity for tissues. So, mordant is necessary to make haematein–mordant complex positive, so that this complex can bind to anionic tissue sites.



FLOWCHART 21.1 Processing of haematoxylin

Classification of haematoxylin

Based on mordant used with haematoxylin:

- *Alum haematoxylin:* Mordant–potash alum (aluminium potassium sulphate) or ammonium alum (aluminium ammonium sulphate), e.g. Ehrlich's haematoxylin, Mayer's haematoxylin, Gill's haematoxylins, Cole's haematoxylin
- *Iron haematoxylin:* Mordant–ferric chloride or ferric ammonium sulphate, e.g. Weigert's haematoxylin, Heidenhain's haematoxylin, Loyez

haematoxylin, Verhoeff's haematoxylin
- *Tungston haematoxylin:* Mordant–phosphotungstic acid
- *Molybdenum haematoxylin:* Mordant–molybdic acid
- *Lead haematoxylin:* Mordant–lead
- *Haematoxylin without mordant*

Eosin

- A red dye, properly used on well-fixed material, stains connective tissue and cytoplasm in varying intensity and shades of primary colour giving a most useful differential stain.
- It is the most suitable stain to combine with alum haematoxylin to demonstrate the histological architecture of tissues.
- It has the ability to distinguish between the cytoplasm of different types of cells and different types of connective tissue fibres and matrices by staining those differing shades of red and pink.
- Types:
 - Eosin Y: Water-soluble, widely used
 - Eosin S: Ethyl eosin—alcohol-soluble
 - Eosin B: Eosin bluish—erythrosin B

H and E staining procedure

Hydrate

1. Xylene—5 minutes
2. Xylene—5 minutes
3. Xylene—5 minutes
4. 100% Alcohol—1 minute
5. 100% Alcohol—1 minute
6. 95% Alcohol—1 minute
7. 95% Alcohol—1 minute
8. 70% Alcohol—1 minute
9. Deionized water—2 minutes

Stain

1. Haematoxylin—2 minutes
2. Wash in running water
3. Bluing solution—1–2 dips
4. Wash in running water

5. 80% alcohol—2 minutes
6. Eosin—2–3 minutes

Dehydrate

1. 80% Alcohol—3–4 dips
2. 95% Alcohol—1 minute
3. 95% Alcohol—1 minute
4. 100% Alcohol—1 minute
5. 100% Alcohol—1 minute
6. Xylene—3 minutes
7. Xylene—3 minutes
8. Xylene—3 minutes

Papanicolaou stain for cytological preparations

It is the universal stain for cytological preparations. Harris haematoxylin is the optimal nuclear stain and the combination of orange-6 (OG-6) and eosin (EA-50) gives the subtle range of green, blue and pink hues to the cell cytoplasm.

Procedure

1. Remove polyethylene glycol fixative in 50% alcohol, 2 minutes
Hydrate in 95% alcohol, 2 minutes, and 70% alcohol, 2 minutes
2. Rinse in water, 1 minute
3. Stain in Harris haematoxylin, 5 minutes
4. Rinse in water, 2 minutes
5. Differentiate in 0.5% aqueous hydrochloric acid, 10 seconds
6. Rinse in water, 2 minutes
7. Blue in Scott's tap water, 2 minutes
8. Rinse in water, 2 minutes
9. Dehydrate:
 - 70% Alcohol, 2 minutes
 - 95% Alcohol, 2 minutes
 - 95% Alcohol, 2 minutes
10. Stain in OG-6, 2 minutes
11. Rinse in 95% alcohol, 2 minutes
12. Rinse in 95% alcohol, 2 minutes
13. Stain in EA-50, 3 minutes

14. Rinse in 95% alcohol, 1 minute

Results

- The nuclei: Blue or black
- Cytoplasm (nonkeratinizing): Blue or green
- Keratinizing cells: Pink or orange

Artifacts

- Artifacts are structures or features in tissue that interfere with normal histological examination. These are not always present in normal tissue and can come from outside sources.
- Artifacts interfere with histology by changing the tissues appearance and hiding structures.
- These can be divided into two categories: pre-tissue preparation and post-tissue preparation.

Pre-tissue preparation

These are features and structures that have been introduced prior to the collection of the tissues. A common example of these includes ink from tattoos and freckles (melanin) in skin samples.

Post-tissue preparation

Artifacts can result from tissue processing. Processing commonly leads to changes like shrinkage, washing out of particular cellular components, colour changes in different tissue types and alterations of the structures in the tissue. Because these are resulted in a laboratory, the majority of post-histology artifacts can be avoided or removed after being discovered. A common example is mercury pigment left behind after using Zenker's fixative to fix a section.

Problems and solutions for paraffin section

Table 21.1 describes problems and solutions for paraffin section.

Table 21.1

Problems and solutions for paraffin section

Causes	Solutions
Ribbon or consecutive sections curved 1. Block edges not parallel 2. Dull blade edge 3. Excessive paraffin 4. Tissue varying in consistency	1. Trim block until parallel 2. Replace blade or move to a different area 3. Trim away excess paraffin 4. Reorient block
Thick and thin sections 1. Paraffin too soft for tissue or conditions 2. Insufficient clearance angle 3. Faulty microtome mechanisms 4. Blade or block loose in holder	1. Remove excess paraffin from the edge of blade 2. Maintain microtome: Lubricate and calibrate; check for obvious faults with microtome; parts may be worn 3. Tighten block and blade 4. Increase clearance angle
***Chatter*: Thick and thin zones parallel to edge** 1. Knife or block loose in holder 2. Excessively steep clearance angle or knife tilt 3. Tissue or paraffin too hard for sectioning 4. Calcified areas in tissue 5. Overdehydration of tissue 6. Dull blade	1. Clean blade edge to remove excess paraffin 2. Replace or use new area of blade 3. Tighten the blade levers 4. Reduce angle 5. Rehydrate and surface decalcify 6. Re-embed in fresh paraffin
Splitting of sections at right angles to knife edge 1. Nicks in blade 2. Hard particles in tissue 3. Hard particles in paraffin	1. Use different part of blade or replace 2. If calcium deposit: Surface decal 3. If mineral or other particle, remove with fine sharp-pointed scalpel
Sections will not form ribbons 1. Paraffin too hard for sectioning conditions 2. Debris on knife edge 3. Clearance angle incorrect	1. Re-embed in lower melting point paraffin 2. Warm surface of block 3. Clean blade and back of blade holder 4. Adjust to optimal angle
Sections attach to block on return stroke 1. Insufficient clearance angle 2. Debris on blade edge 3. Debris on block edge 4. Static electricity on ribbon	1. Increase clearance angle 2. Clean blade edge 3. Trim edges of block 4. Humidify the air around the microtome 5. Place static guard or dryer sheets near microtome
Incomplete section 1. Incomplete impregnation of tissue with paraffin 2. Tissue incorrectly embedded 3. Sections superficially cut	1. Reprocess tissue block 2. Re-embed tissue; make sure orientation is correct and tissue is flat in mould 3. Reface block, cut deeper into the tissue
Excessive compression 1. Dull blade 2. Paraffin too soft for the tissue	1. Replace blade 2. Cool block face and recut
Sections expand or disintegrate on water bath 1. Incomplete tissue processing 2. Water temperature too high in floatation bath	1. Reprocess tissue 2. Turn down the temperature in the floatation bath
Sections roll into a tight coil instead of remaining flat on knife edge 1. Blade dull 2. Rake angle too small 3. Section too thick	1. Use a new blade 2. Reduce blade tilt, if clearance angle is excessive 3. Reduce section thickness

Oral diagnostic cytology

- Exfoliative cytology, also called *cytopathology,* is the study of cells desquamated from the body. These exfoliated cells which are scrapped off by means of specific instruments can be spread over the glass slide and

are fixed in 95% isopropyl alcohol or ethyl alcohol before they dry. Staining is performed and viewed under microscope for diagnosis. This cytodiagnosis procedure was introduced by George N Papanicolau in 1941 as a routine procedure in the detection of cervical cancer.

- Two main methods are used to obtain cells for examination:
 1. Exfoliative cytology
 2. Fine needle aspiration cytology

Indications for cytology

It is indicated in extremely debilitated patients and aid in diagnosis of some dermatological diseases like pemphigus, white sponge naevus, viral lesions, anaemia, oral pre-malignant and malignant lesions. It is also indicated for the patients who had radiation therapy for the malignant lesions.

Exfoliative cytology

- Exfoliative cytology is the study of cells which exfoliate or abrade from the body surfaces.
- The rationale for exfoliative cytology lies in epithelium physiology.
- Normal epithelium undergoes exfoliation of its superficial cells due to physiological turnover. The cells of the deeper layers are adherent to each other normally. When the epithelium becomes the seat of any pathological condition, the cells may lose their cohesiveness and cells in the deeper layer may shed along with the superficial cells. These exfoliated cells as well as cells which are scrapped off by means of specific instruments, can be studied quantitatively and qualitatively.
- Cytology is not a substitute but an adjunct to the surgical biopsy.
- It is a quick, simple, painless and bloodless procedure.
- It helps as a check against false-negative biopsies.
- It is especially helpful in follow-up detection of recurrent carcinoma in previously treated cases.
- It is valuable for screening lesions whose gross appearance is such that biopsy is not warranted.

Procedure

- The surface of the lesion should be cleansed to remove debris and mucin and then vigorously scrap the entire surface of the lesion several times with a metal cement spatula, a moistened tongue blade or a cytobrush.

- The collected material is then quickly spread evenly over a microscopic slide and fixed immediately before the smear dries.
- The fixative may be a commercial preparation such as Spray-Cyte, 95% alcohol or equal parts of alcohol and ether. After the slide is flooded with the fixative, it should be allowed to stand for 30 minutes to air dry.
- Two smears are always submitted from each lesion, since additional staining techniques are frequently employed.

Analysis of cytologic smear

The cytologic smear, usually reported by the cytologist, falls into one of the five classes:

- *Class I (normal):* It indicates that only normal cells are observed.
- *Class II (atypical):* It indicates the presence of minor atypia but no evidence of malignant changes.
- *Class III (intermediate):* This is an in between cytology that separates cancer from non-cancer diagnosis. The cells display wider atypia that may be suggestive of cancer, but they are not clear-cut and may represent precancerous lesions or carcinoma in situ. Biopsy is recommended.
- *Class IV (suggestive of cancer):* A few cells with malignant characteristics or many cells with borderline characteristics. Biopsy is mandatory.
- *Class V (positive for cancer):* Cells those are obviously malignant. Biopsy is mandatory.

It has certain limitations: (i) the presence or extent of the lesion cannot be assessed and (ii) it cannot be considered for the final diagnosis.

Indications

The cytologic smears have been useful in the diagnosis of following lesions:

- Herpes simplex infection
- Herpes zoster
- Pemphigus vulgaris
- Benign familial pemphigus
- Keratosis follicularis
- Hereditary benign intraepithelial dyskeratosis
- White sponge naevus
- Pernicious anaemia
- Sickle cell anaemia

Fine needle aspiration cytology (FNAC)

- It is a percutaneous (through the skin) procedure. It is typically accomplished with a fine gauge needle—22 or 25 gauge.
- The area is cleaned and then usually numbed with a local anaesthetic.
- The needle is placed into the region of abnormality such as cyst or tumour.
- Once the needle is placed, a vacuum is created with the syringe and multiple in and out needle motions are performed.
- The cells to be sampled are sucked into this syringe through the fine needle.
- Three or four samples are usually taken.
- The cellular aspirate is mounted on a glass slide and immediate diagnosis can be made with proper staining and final diagnosis is made. It is used to diagnose the tumours of salivary gland, lymph node pathology and cysts.
- Radiological screening or ultrasonic guidance can be used to direct the needle into a deep-seated lesion.

Immunohistochemistry

Immunohistochemistry (IHC) is the localization of antigens in tissue sections by the use of labelled antibodies as specific reagents through antigen–antibody interactions that are visualized by a marker such as fluorescent dye, enzyme, radioactive element or colloidal gold.

- **Principle:** Immunohistochemical methods are based on the specific interaction of an antibody with tissue antigen followed by localization of the site of binding using a label.
- **Procedure**
 - Fix the tissue for 3–24 hours in formalin and routinely process to paraffin wax.
 - Cut the sections into 3–5 μm thick and place on a cleaned glass slide, if required section adhesive may be used.
 - Dewax sections in xylene and bring to absolute alcohol.
 - Block endogenous peroxidase activity by incubating in 0.5% hydrogen peroxide in methanol for 10 minutes.
 - Rehydrate, wash well in running water and transfer to Tris-buffered saline (TBS).
 - Retrieve the antigens using appropriate antigen retrieval technique.
 - Nonimmune serum is required to block nonspecific staining, especially when polyclonal antibodies are employed for 10 minutes.

- Bring sections to TBS, drain off, wipe around the sections.
- Apply optimally diluted primary antibody for 30–60 minutes.
- Wash slides with TBS.
- Cover slides with optimally diluted peroxidase conjugated secondary antibody.
- Wash slides with TBS.
- Incubate the slides with 3,3′-diaminobenzidine tetrahydrochloride (DAB.4HCl) solution for 10 minutes.
- Rinse in TBS for few minutes.
- Counter stain in haematoxylin, dehydrate, clean and mount.

- Immunohistochemical staining (IHC) is widely used in the diagnosis of abnormal cells such as those found in cancerous lesions.
- Specific molecular markers are characteristic of particular cellular events such as proliferation or cell death (apoptosis).
- IHC is also widely used in basic research to understand the distribution and localization of biomarkers and differentially expressed proteins in different parts of a biological tissue.
- Epithelial markers—cytokeratin
- Mesenchymal markers:
 - Vimentin—most of the mesenchymal cells, lymphoid cells, neural crest cells
 - Desmin, actin, myoglobin—muscle markers
 - S–100, glial fibrillary acidic protein (GFAP), neural filaments, CD 57—neural markers
 - CD31, CD34, factor VIII—endothelial markers
 - HMB45, MART-1, anti-S-100 protein—melanocytic markers.

Key points

- *Biopsy* is the removal of tissue from the living organism for the purposes of microscopic examination and diagnosis.
- *Excisional biopsy:* Total excision of smaller lesion for microscopic study.
- *Incisional or diagnostic biopsy:* A small piece of tissue from larger lesions is removed for microscopic study.
- *Fixation of specimen is* the treatment of biological specimens with chemical solutions to preserve the cellular structure so that it is resistant to damage during subsequent processing steps including dehydration, embedding and sectioning.

- *Tissue processing:* Dehydration of the specimen, infiltration of the specimen with paraffin, embedding the specimen, cutting the sections of the specimen, mounting the cut sections on slides.
- *Artifacts:* Ribbon or consecutive sections curved, thick and thin sections, chatter: thick and thin zones parallel to edge, splitting of sections at right angles to knife edge, sections will not form ribbons, sections attach to block on return stroke, incomplete section, excessive compression, sections expand or disintegrate on water bath and sections roll into a tight coil instead of remaining flat on knife edge.
- *Exfoliative cytology* is the study of cells which exfoliate or abrade from the body surfaces.
- *Immunohistochemistry* is the localization of antigens in tissue sections by the use of labelled antibodies as specific reagents through antigen–antibody interactions that are visualized by a marker such as fluorescent dye, enzyme, radioactive element or colloidal gold.
- *Immunohistochemical markers:* Epithelial markers—cytokeratin and mesenchymal markers—vimentin, desmin, actin, myoglobin, S-100, glial fibrillary acidic protein (GFAP), neural filaments, CD57, CD31, CD34, factor VIII, HMB45, MART-1 and anti-S-100 protein.

Frequently asked questions

1. Fixation of tissue specimens or formaldehyde fixation
2. Tissue processing
3. Haematoxylin and eosin staining of tissue specimens
4. Papanicolaou stain
5. Tissue artifacts
6. Exfoliative cytology
7. Immunohistochemistry

Glossary

Oral pathology represents the confluence of the basic sciences and clinical dentistry. Since it has no methods of its own, knowledge in this field is acquired through the adaptation of methods and disciplines of those sciences basic to dental practice, such as gross and microscopic anatomy, chemistry, microbiology and physiology and through information obtained by clinical histories and observation of patients. Through the science of oral pathology, an attempt is made to correlate human biology with the signs and symptoms of human disease. The oral pathologist attempts to understand oral disease so that it can be properly diagnosed and adequately treated.

- **Aberrancy.** Condition where the salivary glands are found farther than normal from their usual location.
- **Abfraction.** It refers to the loss of tooth structure that results from repeated tooth flexure caused by occlusal stresses.
- **Abrasion.** It is defined as pathologic wearing of tooth due to some abnormal mechanical forces.
- **Abscess.** It is a localized accumulation of pus caused by an infection.
- **Acantholysis.** It is defined as loss of cohesiveness or loss of attachment between the epithelial cells due to loss of intercellular bridges and destruction of desmosomes resulting in widening of intercellular space.
- **Acanthosis.** It is an abnormal thickening of spinous cell layer for a particular location.
- **Agenesis.** It is a complete failure of development of a part.
- **Ameloblastoma.** It is defined as usually unicentric, nonfunctional, intermittent in growth, anatomically benign and clinically persistent.
- **Anaplasia.** It is defined as lack of differentiation.
- **Aplasia.** It is an extreme hypoplasia.
- **Apoptosis.** It is a pathway of a cell death that is induced by a tightly

regulated intracellular program in which cells destined to die, activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins.

- **Atresia.** It is a congenital occlusion or absence of one or more of the major salivary gland ducts.
- **Atrophy.** It is a diminution in size of a part due to a diminution in the number or size of its constituent elements.
- **Attrition.** It is defined as the physiologic wearing of a tooth as a result of tooth to tooth contact as in mastication.
- **Biopsy.** It is the removal of tissue from the living organism for the purposes of microscopic examination and diagnosis.
- **Bullae.** It is a well-circumscribed elevated lesion of the skin or mucosa containing fluid measuring more than 0.5 cm in diameter.
- **Calculus.** It is defined as deposit of inorganic salts composed primarily of calcium carbonate and phosphate mixed with food debris, bacteria and desquamated epithelial cells.
- **Carcinoma.** It is a malignant tumour of epithelial origin.
- **Carcinoma in situ.** It is a lesion in which the full thickness or almost full thickness of spontaneous epithelium shows cellular features of carcinoma without stromal invasion.
- **Cellulitis.** It is a painful swelling of the soft tissue of the mouth and face resulting from a diffuse spreading of purulent exudate along facial planes that separate the muscle bundles.
- **Choristoma.** It is a nonneoplastic tumour-like mass of developmental origin in which there are found tissues foreign to the part of the body.
- **Chronic inflammation.** It is defined as a prolonged process in which destruction and inflammation are proceeding at the same time as attempts at healing.
- **Complex odontoma.** It is a malformation in which all the dental tissues are represented, individual tissues being mainly well formed but occurring in

a more or less disorderly pattern.

- **Compound odontoma.** It is a malformation in which all the dental tissues are represented in a more orderly pattern so that the lesion consists of many tooth-like structures. Most of these structures do not morphologically resemble the teeth of the normal dentition, but in each enamel, dentine, cementum and pulp are arranged as normal tooth.
- **Cyst.** It is a pathological cavity lined by epithelium containing fluid or semisolid material but not pus.
- **Dental caries.** It is defined as a progressive irreversible microbial disease of multifactorial nature affecting the calcified tissues of the teeth characterized by demineralization of the inorganic portion and destruction of organic portion of the tooth.
- **Dental plaque.** It is a specific but highly variable structural entity resulting from colonization of microorganism on tooth surface, restorations and other parts of oral cavity, consisting of salivary components like mucin, desquamated epithelial cells, debris and microorganisms all embedded in gelatinous extracellular matrix.
- **Differentiation.** It refers to the extent to which neoplastic cells resemble comparable normal cells both morphologically and functionally.
- **Dystrophy.** It is defined as a disorder, usually congenital, of the structure or function of an organ or tissue due to its perverted nutrition.
- **Ecchymosis.** It is large purpuric lesions.
- **Epithelial dysplasia.** It is a precancerous lesion of stratified squamous epithelium characterized by cellular atypia and loss of normal maturation and stratification.
- **Epithelium.** It is an avascular tissue in which cells are closely packed with minimal intercellular substance and always separated by connective tissue by basement membrane which helps in diffusion of tissue fluid for nourishment.
- **Erosion (hard tissue).** It is defined as a loss of tooth structure by a chemical process that does not involve known bacterial action.

- **Erosion (soft tissue).** It is a shallow excavation of skin or mucosa due to incomplete loss of epidermis or epithelium where basal layer is intact and connective tissue is not exposed.
- **Fibrous dysplasia.** It is a benign self-limiting but encapsulated lesion occurring mainly in young subjects, usually in the maxilla and showing replacement of the normal bone by a cellular fibrous tissue containing islands or trabeculae of metaplastic bone.
- **Genodermatosis.** It is a hereditary skin disorder which is also accompanied by various systemic manifestations of different altered enzyme functions.
- **Granuloma.** It consists of microscopic aggregation of macrophages that are transformed into epithelium-like cells surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells.
- **Granulomatous inflammation.** It is defined as a special variety of chronic inflammation in which cells of mononuclear phagocyte system are predominant and take the form of macrophages, epithelioid cells and multinucleated giant cells with formation of new blood vessels and proliferation of fibroblasts.
- **Gumma.** It is the scattered foci of granulomatous inflammation presenting as an indurated nodular, ulcerated lesion often associated with tissue destruction in tertiary syphilis.
- **Hamartoma.** It is a tumour-like malformation in which the tissues of a particular part of the body are arranged haphazardly, usually with an excess of one or more of its components.
- **Healing.** It is the body's replacement of destroyed tissue by living tissue.
- **Hyperplasia.** It is the increase in size of an organ or tissue due to an increase in the number of its specialized constituent cells.
- **Hypertrophy.** It is the increase in size of an organ or tissue due to increase in size of its constituent specialized cells.
- **Hypoplasia.** It is a failure of development to a full mature size.

- **Inflammation.** It is the reaction of the vascular and supporting elements of a tissue to injury and results in the formation of a protein-rich exudate provided the injury has not been so severe as to destroy the area.
- **Leukoplakia.** It is a raised white patch of mucosa measuring more than 5 mm in diameter which could not be scrapped off and which cannot be attributable to any other diagnosable disease.
- **Macule.** It is a well-circumscribed flat lesion that is noticeable because of its change from normal skin colour.
- **Metaplasia.** It is a condition in which there is a change of one type of differentiated tissue to another type of similarly differentiated tissue.
- **Naevus.** It is a hamartomatous tumour-like malformation derived from neural crest cells called *naevus cells*.
- **Necrosis.** It refers to spectrum of morphologic changes that follow cell death in a living tissue largely resulting from the progressively degradation action of enzymes on the lethally injured cell.
- **Nodule.** It is a lesion present deep in the dermis and epidermis that can be easily moved over them.
- **Oral submucous fibrosis.** It is defined as a chronic insidious disease affecting any part of the oral cavity and sometimes pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxtaepithelial inflammatory reaction followed by fibroelastic change of the lamina propria with epithelial atrophy leading to stiffness of the oral mucosa causing trismus and difficulty in eating.
- **Osteomyelitis.** It is defined as an inflammatory condition of bone that begins as infection of medullary cavity and haversian system and extends to involve periosteum.
- **Papule.** It is a solid lesion raised above the skin surface that is smaller than 0.5 cm in diameter.
- **Patch.** It is discolouration of skin or mucosa up to 5 mm and not raised from surface.

- **Pemphigus.** It is a group of potentially life-threatening autoimmune mucocutaneous disease characterized by epithelial blistering in cycles affecting cutaneous and/or mucosal surface.
- **Petechiae.** These are purple lesions measuring 1–2 mm in diameter.
- **Plaque.** It is a solid raised lesion that is more than 0.5 cm in diameter.
- **Pleomorphism.** It is a variation in size and shape of the cells.
- **Precancerous condition.** It is a generalized pathological state of oral mucosa associated with significantly increased risk of cancer.
- **Precancerous lesion.** It is morphologically altered tissue in which cancer is most likely to occur than its apparently normal counterpart.
- **Purpura.** It is reddish to purple, flat lesion caused by blood from vessels leaking into the subcutaneous tissue.
- **Pustules.** These are raised lesions containing purulent material.
- **Quid.** It is a substance or mixture of substances placed in the mouth or chewed and remains in contact with the mucosa usually containing one or both of the two basic constituents—tobacco and/or areca nut in raw or any manufactured or processed form.
- **Sarcoma.** It is a malignant tumour of connective tissue origin.
- **Squamous cell carcinoma.** It is defined as a malignant epithelial neoplasm exhibiting squamous differentiation as characterized by the formation of keratin and/or the presence of intercellular bridges.
- **Teratoma.** It is a tumour consisting of multiple tissues foreign to the part from which it arises. Tissue representative of the three primitive germinal layers may be found.
- **Tumour.** It is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change.
- **Ulcer.** It is an excavation of mucosa or skin due to loss of epithelium as a result of necrosis or cell death causing exposure of underlying connective

tissue.

- **Vesicle.** It is a well-circumscribed elevated lesion of the skin or mucosa containing fluid measuring less than 0.5 cm in diameter.

Appendices

Appendix A differential diagnosis of oral and maxillofacial diseases

Table A.1

Mucosal and soft tissue pathology

PART I: Mucosal and soft tissue pathology: Colour changes	
Lesion or condition	**Special characteristics**
White lesions—can be scraped off • White-coated tongue • Pseudomembranous candidiasis • Thermal burn • Sloughing traumatic lesion • Toothpaste or mouthwash reaction • Secondary syphilis • Diphtheria	• May be scraped off slightly, with difficulty • Milk curd or cottage cheese appearance; may leave red • Surface can be peeling off • Surface may appear to be peeling off • Filmy whiteness; leaves normal appearing mucosa when rubbed off • Mucous patch; may be only partially scraped off • Grey-white pseudomembrane of oropharynx
White lesions—cannot be scraped off • Linea alba • Leukoedema • Leukoplakia • Tobacco pouch keratosis • Actinic cheilosis • Lichen planus • White coated tongue • Nicotine stomatitis • Hyperplastic candidiasis • Lupus erythematosus • Submucous fibrosis • White sponge naevus • Tertiary syphilis	• Buccal mucosa along occlusal plane • Milky white alteration of buccal mucosa, bilaterally; disappears when stretched • May show benign hyperkeratosis, epithelial dysplasia or invasive carcinoma • Usually in mandibular vestibule; associated with use of snuff or chewing tobacco • Pale, grey-white, scaly alteration of lower lip; usually in older men with history of chronic sun exposure • Wickham's striae; typically bilateral on buccal mucosa • Diffuse involvement of dorsal tongue • Usually associated with pipe smoking; occurs on hard palate • Most commonly affects anterior buccal mucosa • Most common on buccal mucosa; may mimic lichen planus or leukoplakia; associated skin lesions usually present • More common in South Asia; associated with betel quid chewing • Hereditary; onset in childhood; generalized lesions, especially on buccal mucosa • Syphilitic glossitis
White and red lesions • Erythema migrans • Candidiasis • Lichen planus • Burns • Actinic cheilosis • Nicotine stomatitis • Erythroleukoplakia • Lupus erythematosus • Scarlet fever • Verruciform xanthoma	• Geographic tongue; continually changing pattern; rarely involves other oral mucosal sites • White component may be rubbed off • Atrophic or erosive forms; Wickham's striae; typically bilateral on buccal mucosa • White component may be rubbed off • Pale, grey-white and red alteration to lower lip; usually in older men with history of chronic sun exposure • Usually associated with pipe smoking; occurs on hard palate • Usually shows epithelial dysplasia or carcinoma • Most common on buccal mucosa; may mimic lichen planus or leukoplakia; associated skin lesions usually present • Secondary to β-haemolytic streptococcal infection; strawberry/raspberry tongue • Most common on gingiva and hard palate; surface may be papillary
Red lesions • Traumatic erythema • Denture stomatitis • Erythematous candidiasis • Erythema migrans • Angular cheilitis • Erythroplakia • Haemangioma • Lupus erythematosus • Scarlet fever • Plasma cell gingivitis • Radiation mucositis	• Caused by local irritation • Denture-bearing palatal mucosa • Central papillary atrophy (median rhomboid glossitis) • Geographic tongue, continually changing pattern; rarely involves other mucosal sites • Erythema and cracking at labial commissures • Usually shows epithelial dysplasia or carcinoma • Develops in younger patients; may blanch; may show bluish hue • Usually associated with skin lesions • Secondary to β-haemolytic streptococcal infection; strawberry/raspberry tongue • Allergic reaction usually related to flavouring agents • Patient currently undergoing radiotherapy

Table A.2

White lesions

Scrapable lesions	Non-scrapable lesion
Slough, pseudomembranous, necrotic lesions • Physical agents • Traumatic ulcer • Chemical burns • Thermal burns • Habitual cheek and lip biting • Cotton roll injury • Iatrogenic lesions • Infections • Bacterial • Secondary, tertiary syphilis • Tuberculosis ulcer • Diphtheritic ulcers • ANUG • Cancrum oris • Viral • Herpes simplex • Chickenpox • Smallpox • Measles • Fungal • Candidiasis • Histoplasmosis	*Hyperkeratotic lesions* • Normal variants • Linea alba • Leukoedema • Fordyce granules • Developmental • Dyskeratosis congenita • Pachyonychia congenita • Keratosis follicularis • Psoriasis • White spongy naevus • Acanthosis nigricans • Reactive lesions • Frictional keratosis • Leukoplakia • Tobacco pouch keratosis • Nicotine stomatitis • Benign/malignant lesions • Papillomas • White exophytic squamous cell carcinoma • Verrucous carcinoma • Autoimmune disorders • Lichen planus • Lichenoid reaction • Lupus erythematosus

Table A.3

Red lesions

1. **Inflammatory condition**
 - *Inflammation associated with traumatic injury:*
 - Mechanical: Cheek biting, ill-fitting denture
 - Chemical: Aspirin, formocresol
 - Thermal: Hot food and beverage, iatrogenic heat
 - Radiation: Mucositis, cheilitis
 - *Infections:*
 - Bacterial: Pharyngitis, tonsillitis, scarlet fever, ANUG
 - Fungal: Acute pseudomembranous candidiasis, atrophic candidiasis, angular cheilitis
 - Viral: Herpes infection, chickenpox, measles, herpangina
 - *Allergic/immunological disorders:*
 - Peripheral giant cell granuloma
 - Pyogenic granuloma
 - Desquamative gingivitis
 - Traumatic haemangioma
2. **Congenital, hereditary/developmental condition**
 - Geographic tongue
 - Hereditary haemorrhagic telangiectasia
 - Haemangioma
 - Melkersson–Rosenthal syndrome
 - Sturge–Weber syndrome
 - Crohn's disease
3. **Vascular disease**
 - Purpura
 - Leukaemia
 - Polycythaemia
 - Agranulocytosis
4. **Dermatological**
 - Lichen planus
 - Lichenoid reaction
 - Pemphigus
 - Erythema multiforme
 - Stevens–Johnson syndrome
 - Epidermolysis bullosa
 - Lupus erythematosus
5. **Permanent and malignant lesions**
 - Atrophic leukoplakia
 - Erythroplakia
 - Squamous cell carcinoma
 - Kaposi's sarcoma
6. **Other systemic disease**
 - Diabetes stomatitis
 - Ulcerative stomatitis
 - Uraemic stomatitis
 - Scurvy
 - Pernicious anaemia

Table A.4

Red and white lesions

- **Red lesions with keratotic component**
 - Chronic mechanical trauma
 - Migratory glossitis
 - Nicotine stomatitis
 - Erosive lichen planus and lichenoid reaction
 - Speckled leukoplakia and erythroplakia
 - Squamous cell carcinoma
 - Lupus erythematosus
- **Red lesions with necrotic component**
 - Chemical and drug burns
 - Thermal burns
 - Aphthous ulcers and stomatitis
 - Pseudomembranous candidiasis
 - ANUG
 - Allergic mucositis
 - Radiation mucositis
 - Pyogenic granuloma
- **Vesiculobullous lesions**
 - Primary and secondary herpes simplex
 - Benign mucous membrane pemphigoid
 - Erythema multiforme
 - Pemphigus
 - Lichen planus

Table A.5

Vesiculobullous lesions (depending on the location of split)

Intraepithelial split (*suprabasilar split*)	Subepithelial split (*sub-basilar split*)
• Pemphigus • Epidermolysis bullosa simplex • Darier's disease • Familial benign pemphigus • Erythema multiforme	• Bullous pemphigoid • Cicatricial pemphigoid • Epidermolysis bullosa (junctional and dystrophic) • Systemic lupus erythematosus • Dermatitis herpetiformis

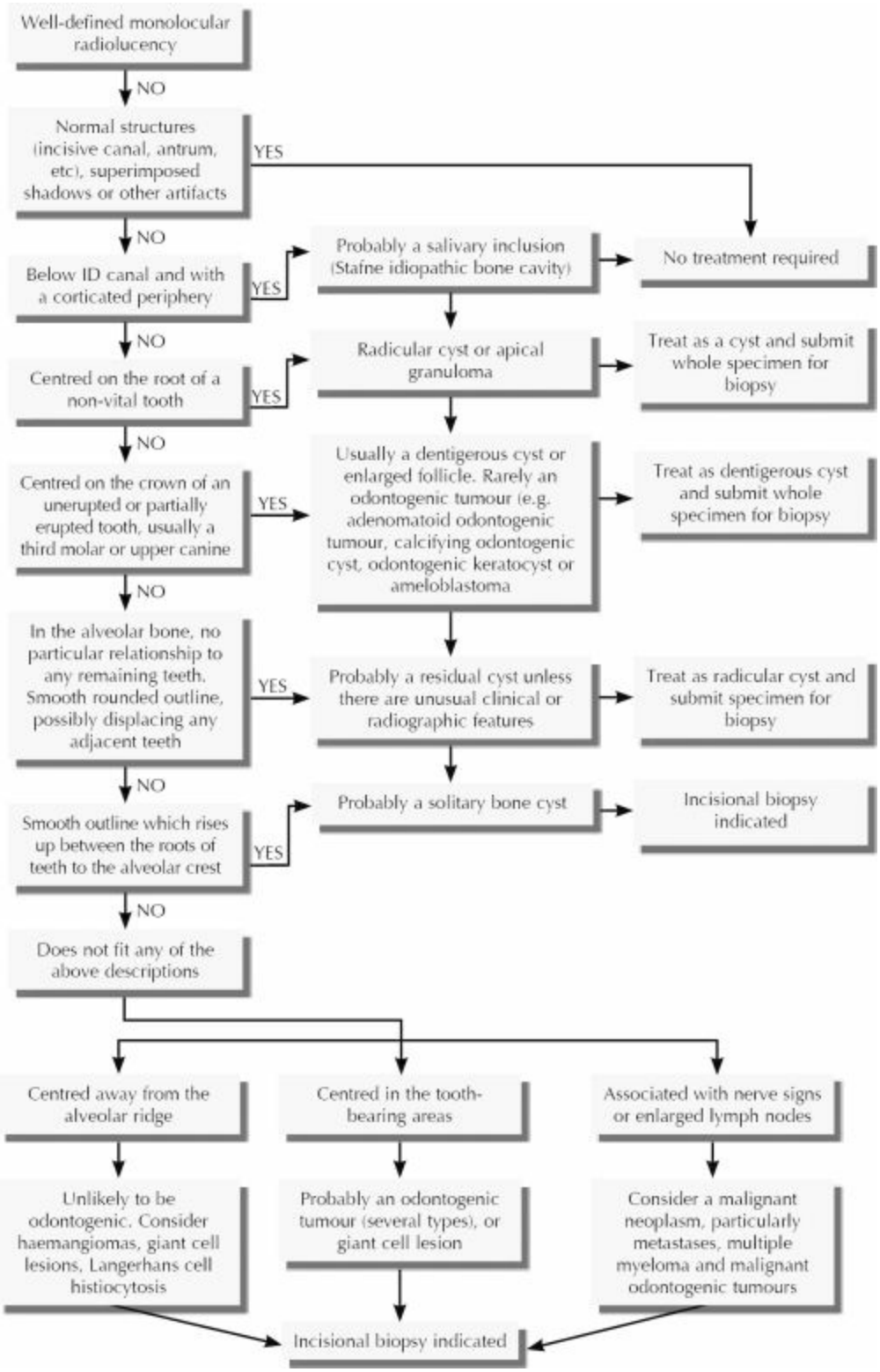
Table A.6

Normal haematocrit values

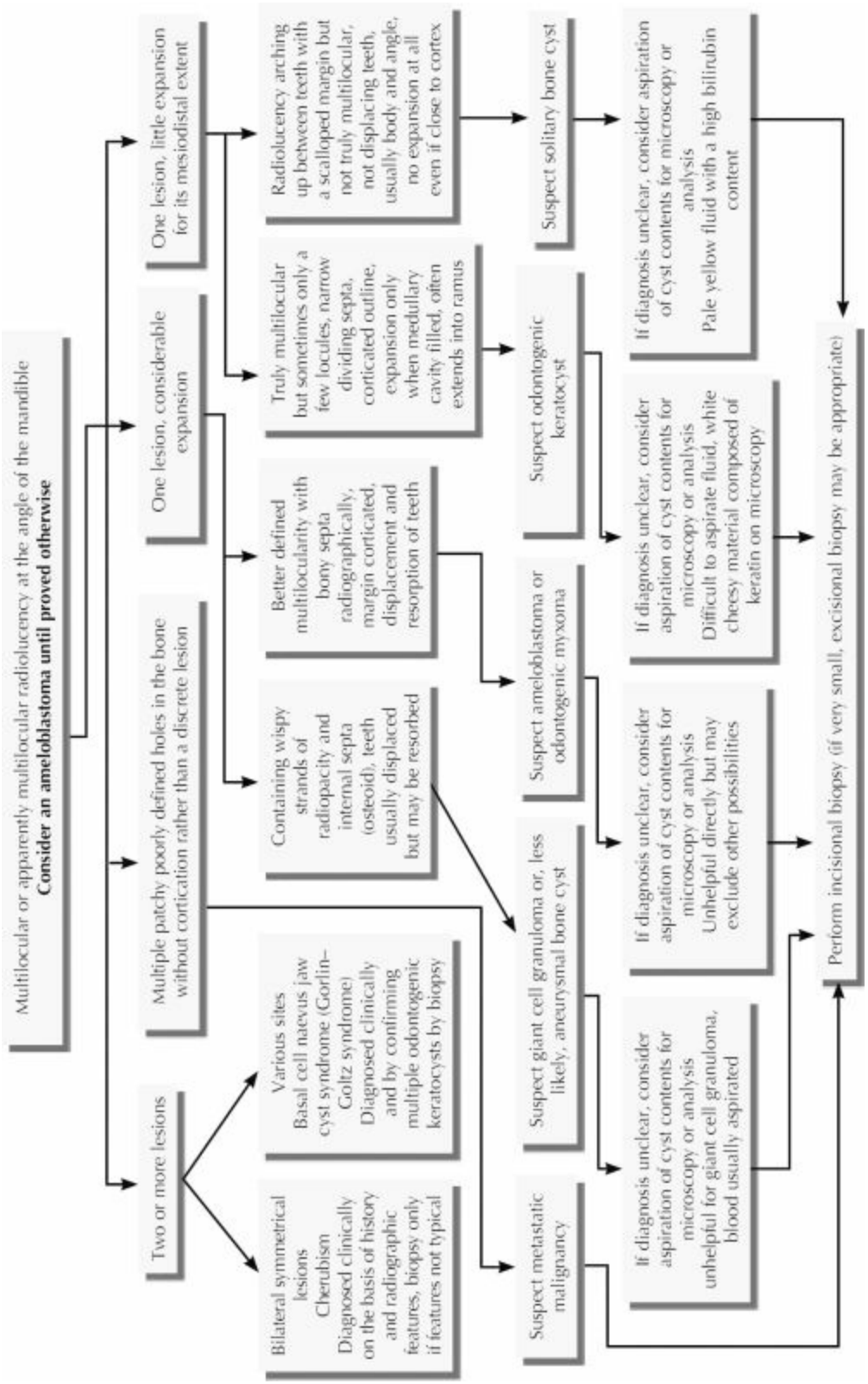
Component	Reference value
Erythrocyte and haemoglobin	
Erythrocyte count • Males • Females	$4.5–6.5 \times 10^{12}$/l $3.8–5.8 \times 10^{12}$/l
Erythrocyte diameter	6.7–7.7 μm
Erythrocyte thickness • Peripheral • Central	2.4 μm 1.0 μm
Erythrocyte indices • Mean corpuscular haemoglobin (MCH) • Mean corpuscular volume (MCV) • Mean corpuscular haemoglobin concentration (MCHC)	27–32 pg 77–93 pg 30–35 g/dl
Erythrocyte lifespan	120 days
Erythrocyte sedimentation rate (ESR) • Westergren 1st hr, males • Females • Wintrobe, 1st hr, males • Females	0–15 mm 0–20 mm 0–9 mm 0–20 mm
Haemoglobin • Adult haemoglobin • Males • Females • Fetal haemoglobin	13–18 g/dl 11.5–16.5 g/dl 16–18 g/dl
Leukocytes	
Total leukocyte count • Adult • Infants	4000–11000/dl 10000–25000/dl
Differential leukocyte count • Neutrophils • Eosinophils • Basophils • Monocyte • Lymphocyte	40–75% (2000–7500/μl) 1–6% (40–400/μl) <1% (10–100/μl) 2–10% (200–800/μl) 20–50% (1500–4000/μl)
Platelets and coagulation	
Platelet count	150000–400000/μl
Bleeding time • Ivy's method • Template method	2–7 min 2.5–9.5 min
Clotting time • Lee and White method	4–9 min at 37°C

Appendix B differential diagnosis (flowcharts)

FLOWCHART B.1 Differential diagnosis and management of sharply defined mixed radiolucencies in the jaws



FLOWCHART B.2 Differential diagnosis of the common and important causes of a welldefined monolocular radiolucency in the jaws



FLOWCHART B.3 Differential diagnosis of a multilocular radiolucency at the angle of the mandible

Index

A

Abrasion of teeth, 336–337

Abscess, 251–252, 286–287, 289–290, 459

 dentoalveolar, 286

 gingival, 242

 lateral periodontal, 251–252

 Monro's, 459

 periapical, 286–287, 289–290

 periodontal, 251–252

 pulp, 281

Abtropfung effect, 35

Acantholytic cells, 466

Acanthosis, 198, 426, 453

 nigricans, 426, 453

Achondroplasia, 429–430

Acidogenic theory of dental caries, 253–258

Acinic cell carcinoma, 114–115, 117

Acral lentiginous melanoma, 53–55

Acrodynia, 330–331

Acromegaly, 391

Actinomycosis, 190–192

Acute necrotizing ulcerative gingivitis, 251, 292, 380

Addison's disease, 226, 401–402, 421

Adenoid cystic carcinoma, 98, 111–113, 114t

Adenoma, 103, 116
basal cell, 104–105
canalicular, 105
oxyphilic, 103–104
pleomorphic, 96, 99–101, 115–116
Adenomatoid odontogenic tumour, 136–138, 138f
Aerodontalgia, 279
African jaw lymphoma, 87–88
Agnathia, 14
AIDS (acquired immune deficiency syndrome), 216
Albright's syndrome, 434
Alkaline phosphatase, 352, 363, 423
Allergy, 237, 322, 324, 405
denture material, 322
effects on oral tissues, 324
Alveolar osteitis, 355
Alveolitis sicca dolorosa, 355
Amalgam, 312, 331
Ameloblastic carcinoma, 150–151
Ameloblastic fibrodentinoma, 129, 142–143
Ameloblastic fibroma, 129, 141–142
Ameloblastic fibro-odontoma, 129, 143–144
Ameloblastic fibrosarcoma, 129, 152–153
Ameloblastic sarcoma, 152
Ameloblastoma, 129, 149–150, 160
Amelogenesis imperfecta, 21, 23–24
Amyloidosis, 5, 367–368

Anachoretic effect, 186
Anaemia, 479, 482, 487, 498, 503
 aplastic, 479, 498
 classification of, 479
 Cooley's, 485
 erythroblastosis fetalis, 487
 haemolytic, 483–484
 iron deficiency, 479
 Plummer–Vinson syndrome, 481
 sickle cell, 483
 thalassaemia, 486
Aneurysmal bone cyst, 148, 155f, 175
Angina, 239, 306
 Ludwig's, 306
 Vincent's, 239
Angioedema, 413–414
Angioneurotic oedema, 413
Angular cheilitis, 218, 221t, 480
Ankyloglossia, 6
Ankylosed teeth, 23
Ankylosis, temporomandibular joint, 440–443
Anodontia, 15–16
Antoni bodies, 73–74
Apert syndrome, 426–427
Aphthous ulcers, 406f, 408t
Apical periodontal cyst, 171, 343
Apical periodontitis, 277f, 285, 288–289

Aplasia, enamel and dentine, 9, 438
mandibular condyle, 438
salivary glands, 9
Argyria, 331
Arthritis, 190, 409, 442
Ascorbic acid, 351, 384
Asteroid bodies, 411
Atresia, salivary gland duct, 10
Atrophy, muscle, 15, 476
Attrition of teeth, 313, 335–336, 335f
Atypical facial neuralgia, 510–511
Auriculotemporal syndrome, 507–509
Auspitz sign, 458

B

Bacterial infections, 183–203
actinomycosis, 190–192
botryomycosis, 191, 192–193
cancrum oris, 199–200
diphtheria, 199
gonorrhoea, 197–198
leprosy, 188–190
lock jaw, 193–194
lues, 194–197
noma, 199–200
pyogenic granuloma, 201–203
sarcoidosis, 410–412

scarlet fever, 183–184
syphilis, 194–197
tetanus, 193–194
tuberculosis, 184–188
Bacterial plaque, 243, 245–246, 249
dental caries, 253–276
periodontal disease, 235, 490
Ballooning degeneration, 206
Basal cell adenoma, 98, 104
Basal cell carcinoma, 51–52, 111–113, 156
Behcet's syndrome, 406, 408–409, 540–544t
Bell's palsy, 505–506
Bence Jones protein, 84
Benign cementoblastoma, 129, 149
Benign migratory glossitis, 260
Benign mucous membrane pemphigoid, 241, 468, 545t
Benign osteoblastoma, 67–68
Beriberi, 376–384
Biopsy, 352–353, 524–527, 532
exfoliative cytology, 524, 532
technique, 524
types of, 351, 352–353, 524
Biotin, 381–382
Bis-biguanides, 271–272t
Bismuth, 331–332, 334
Bismuth line, 329, 332, 334
Bite mark, 518–519

Blastomycosis, 226
North American, 224–226
South American, 226
Blood dyscrasias,
agranulocytosis, 489
anaemia, 484–485
Chediak-Higashi syndrome, 490–491, 502
Christmas disease, 499, 502
cyclic neutropenia, 489–490, 502
granulocytopenia, 420
haemophilia, 499
infectious mononucleosis, 491–492, 498
leukaemia, 492–495
leukocytosis, 491
leucopenia, 488
neutropenia, cyclic, 489
polycythaemia, 486–487, 545t
purpura, 496, 497
thrombocythaemia, 498–499
thrombocytopaenic purpura, 219
von Willebrand's disease, 501
Blue naevus, 35–36
Blue sclera, 415, 444
Bohn's nodules, 162–163
Bone, fracture healing, effects on, 291–299, 357–359
X-ray radiation, effects on, 326, 439
Borrelia vincentii, 199, 239

Botryoid rhabdomyosarcoma, 91, 92
Botryomycosis, 191, 192–193
Brittle bone disease, 415
Bruxism, 313–314
Bullous pemphigoid, 467–468
Burkitt's lymphoma, 86
Burning mouth syndrome, 507

C

Café-au-lait spots, 72, 433, 434
 fibrous dysplasia, 434
 neurofibromatosis, 73
Caffey's disease, 298
Calcification, calcinosis, 342, 364
 diffuse, of pulp, 342
 dystrophic, 364–365
 metastatic, 365
 pathologic, 364–365
 pulp, 279
Calcifying epithelial odontogenic tumour, 139–141
Calcifying odontogenic cyst, 155f, 167–169
Calcinosis cutis, 476, 477
Calcitonin, 157f, 362, 424
Calculus, 237, 536
Callus, fracture, 298
Canalicular adenoma, 105
Cancrum oris, 199–200, 544t

Candida albicans, 44, 219, 400
Candidiasis, 220
Carbohydrates, dental caries, 254, 256
Carcinoma, 43–47, 50, 108–111, 151–152, 458
 basal cell, 51–52, 111–113, 158
 clear cell, 98, 151
 epidermoid, 43, 108–111, 151
 intraepithelial, 459, 463
 mucoepidermoid, 98, 108–111
 squamous cell, 43–47
 verrucous, 50–51
Carcinoma in situ, 38, 40, 93, 116, 536
Caries, dental, 253–276
 acidogenic theory, 253–257
 acids, 256–257
 acute, 254, 262t
 aetiology of, 258–261
 alexidine, 271–272t
 ammonia, 253, 260
 arrested, 262t, 265
 carbohydrates, 254, 260
 chronic, 262t, 264
 classification of, 261–265
 control and prevention of, 271, 273
 dental plaque, 255, 256, 260
 dentifrices, 271–272t
 dentine, 262t, 267–269, 268f

dextran, 256f, 271–272t
diet, 259t, 261
enamel, 254, 257, 262t, 265–267
enamel hypoplasia, 261
enamel remineralization, 253, 260
fluorine, 259t, 271–272t
glucan, 256f
histopathology of, 265–269, 268f
liquefaction foci, 268
methods of control, 271
microorganisms, 253, 254–256
Miller's theory of, 254–257
morphology and, 259
mouthwashes, 239
nursing bottle, 262t, 264
penicillin, 271–272t
phosphated diets, 271–272t
pit and fissure, 255t, 261, 262t, 267
position, 259
prophylaxis, 271–272t
proteolysis–chelation theory, 257–258
proteolytic theory, 257
radiation, 265
radiographic diagnosis of, 269–270t
recurrent, 262t, 264
root, 255t, 264
saliva, 259–261

secondary, 256, 264
smooth surface, 255t, 262t, 264, 265–267
tooth composition and, 259
vitamin A and, 261
vitamin B and, 374
vitamin C and, 246, 374, 385
vitamin D and, 385
vitamin K and, 271–272t
Cat scratch disease, 200–201
Cavernous sinus thrombosis, 306–307
Cavity preparation, effects on tooth, 310, 311
Cell, acantholytic, 466
gargoyle, 370
Hurler, 369t, 370
lacunar, 89, 345
Reed-Sternberg, 89
ribbon, 527, 531–532t, 531–532t
strap, 92, 93
Tzanck, 207, 463
Cellulitis, 300–301
Cemental dysplasia, periapical, 438
Cementicles, 346–347
Cementifying fibroma, central, 433
Cementoblastoma, benign, 149, 435
Cementoma, 149, 296, 435
Cemento-ossifying fibroma, central, 147, 433, 435
Central giant cell granuloma, 59, 148, 174

Chancre, 195
Chediak–Higashi syndrome, 490–491, 502
Cheilitis, angular, 10, 218, 480, 540–544t
 pachyonychia congenita, 450, 452
 riboflavin deficiency, 12
Cheilitis glandularis, 10–11, 97
Cheilitis granulomatosa, 11
Cheiloscopy, 517
Chemical injuries, 310–334
 acrodynia, 330–331
 allergic reactions, 313
 amalgam tattoo, 331
 argyria, 331
 arsenic, 332
 aspirin, 328
 bismuth, 331–332
 contact stomatitis, 328
 dilantin, 333
 lead, 329
 mercury, 329–330
 pink disease, 330
 plumbism, 329
 silver, 331
 tetracycline, 332–333
Chemoparasitic theory of dental caries, 253
Cherubism, 424–425, 434
Chickenpox, 207–208

Chlorhexidine, dental caries, 238
Chlorophyll, dental caries, 271–272t
Cholesterol clefts, 173f
Chondroectodermal dysplasia, 430, 446–447
Chondroma, 66
Chondrosarcoma, 80–81
Christmas disease, 499, 502
Chronic atrophic candidiasis, 7
Chronic desquamative gingivitis, 241–242
Chronic pemphigus, familial benign, 453, 462
Chvostek's sign, 364, 398
Cicatricial pemphigoid, 241, 468–469
Civatte bodies, 457, 457f
Clear cell carcinoma, of salivary glands, 98, 115
Cleft lip, 10, 12–13
Cleft palate, 10, 12–13
Cleft tongue, 6
Cleidocranial dysplasia, 430–431
Coccidioidomycosis, 226, 227
Collagen diseases, 368
Colloid bodies, 457
Commissural lip pits, 10
Common wart, 32
Compound naevus, 34, 35
Concrescence of teeth, 18
Condensing osteitis, 285, 295
Congenital epulis of newborn, 540–544t

Congenital lip pits and fistulas, 10
Congenital syphilis, 27, 28, 194–197
Contact stomatitis, 462
Cooley's anaemia, 485
Coombs test, 487, 498
Corps ronds, 452, 467
Cotton-wool appearance of bone, 296, 423
Coup de sabre lesion, 15, 475–476
Coxsackie virus, 210
Craniofacial dysostosis, 426
Craniofacial fibrous dysplasia, 434
Craniosynostosis syndromes, 426
CREST syndrome, 476, 477
Cretinism, 394
Crime investigations, 516
 bite marks, 516, 518
 DNA samples, 520, 521
Crocodile tears, 508
Crohn's disease, 246–247, 384, 481
Crouzon disease, 426
Cryptococcus neoformans, 228, 231t, 232
Cushing's syndrome, 402, 404
Cyclic neutropenia, 405, 489–490
Cylindroma, 111–113
Cyst, aneurysmal bone, 148, 155f, 175
 apical periodontal, 171
 benign lymphoepithelial, 121, 180

Bohn's nodules, 162
botryoid odontogenic, 163
branchial cleft, 9, 180
calcifying epithelial odontogenic, 129, 139–141
cervical lymphoepithelial, benign, 9
dental lamina, of newborn, 162
dentigerous, 158
dermoid, 180
epidermoid, 181
Epstein's pearls, 162
eruption, 161–162
extravasation, 178
Gardner's syndrome, 16, 17b, 146
gingival, 161, 162b
Gorlin's, 447
incisive canal, 169
inclusion, 162
keratocyst, odontogenic, 156–159, 167, 170
lateral periodontal, 163–164
median palatal, 170
mucous retention, 178
nasoalveolar, 170–171
nasolabial, 170–171
nasopalatine duct, 169–170
odontogenic, classification of, 155–156
odontogenic keratocyst, 156–159
paradental, 156, 172

periapical, 171
periodontal, 163–164, 163f, 166
primordial, 156
radicular, 171–174
ranula, 178, 179–180
residual, 171, 174
solitary bone, 174–176, 318
surgical ciliated, 180
thyroglossal duct, 180–181
traumatic, 175f, 315
Cytokeratins, 534, 535
Cytologic smear, 209
Cytology, oral exfoliative, 532–533
Cytomegalic inclusion disease, 204

D

Darier's disease, 546t
Darling's disease, 229
Dead tracts of dentine, 339
Dens evaginatus, 19
Dens in dente, 19
Dens invaginatus, 19–20
Dental identification, 335–336
Dental lamina cyst of the newborn, 162
Dental plaque, dental caries and, 255, 256, 260, 265
formation, 257, 258, 260
periodontal disease, 23

Denticles, 146, 341
Dentifrices, abrasion and, 271–272t, 336
 dental caries and, 253
Dentigerous cyst, 22, 134, 136, 158
Dentine, 24, 25–26, 339
 caries of, 265, 267
 dead tracts, 339
 dysplasia, 25–26
 globular, 139
 hypocalcification, 24
 osteodentine, 340
 reparative, 339–340
 sclerosis, 338–339
 secondary, 339–340
 tertiary, 339
Dentinogenesis imperfecta, 24–25, 416
Dentoalveolar abscess, 286
Denture injuries, 321–322
 allergy, denture material, 322, 324
 denture stomatitis, 322
 epulis fissuratum, 323
 generalized inflammation, 321, 322–323
 hyperplasia, 323
 inflammatory hyperplasia, 323
 traumatic ulcer, 321
Dermoid cyst, 180
Desquamative gingivitis, 240, 241–242

Diabetes insipidus, 401
Diabetes mellitus, 237, 248, 398–401
periodontal disease, 219, 235–236, 400
phycomycosis, 231
wound healing, 352–353
xerostomia, 124–125, 400
Diet, dental caries and, 261
carbohydrate content of, 254, 261
fluorine content of, 259t, 271–272t
physical nature of, 261
Dilaceration of teeth, 20
Dilantin, gingival hyperplasia, 237
Dislocation, temporomandibular joint, 440
Donovan bodies, 199
Down syndrome, 431–432
Drug allergy, 329–333
Dry socket, 329–333, 355–356
Ductal papilloma, 106–107
Dyskeratosis, 450, 452–453
congenital, 450
follicularis, 452–453
hereditary benign intraepithelial, 533
Dysplasia, cleidocranial, 23–24, 25–26
dentine, 24, 25
epithelial, 33, 36, 38, 39f
fibrous, monostotic, 350, 433–435
polyostotic, 434

hereditary ectodermal, 430
Dystrophic calcification, 364–365
Dystrophy, muscle, 511–512

E

Ectodermal dysplasia, 15, 19
Ehlers–Danlos syndrome, 340, 448
Elephantiasis gingivae, 247
Ellis–van Creveld syndrome, 430, 446
Embedded teeth, 22
Enamel, 23–24, 26–30, 262t, 265–267
caries, 262t, 265–267
cuticle, 254
hypoplasia, 26
birth injuries, 28
congenital syphilis, 27
dental caries, 267–269
environmental, 27
exanthematous fevers, 27–28
fluoride, 29
hypocalcaemia, 27
hypoparathyroidism, 27
local infection or trauma, 28–29
nutritional deficiency, 27–28
Endocrine metabolism, 361, 398
adrenal, 401–404
disturbances in, 367–368

pancreatic, 398–401
parathyroid, 395–398
pituitary, 391–393
thyroid, 393–395
Eosin, 528–529
Eosinophilia, 284, 320–321
Eosinophilic granuloma, 370
Epidemic parotitis, 216
Epidermoid carcinoma, 43, 108–111, 151
clinical staging, 45t
of buccal mucosa, 48, 540–544t
of gingiva, 43, 49
of lip, 45, 47
of maxillary sinus, 307–308
of palate, 43, 49
of salivary glands, 108–117
of tongue, 44
primary intraosseous, 129, 151–152
Epidermoid cyst, 180
Epidermolysis bullosa, 470
Epithelial dysplasia, 36
Epithelial odontogenic tumour, benign, 139, 151
Epstein–Barr (EB) virus, 49, 85, 88, 89, 95
Epstein's pearls, 162
Epulis, congenital, of the newborn, 163, 540
Erosion of teeth, 337, 338
Eruption, tooth, delayed and premature, 22

cyst, 160–161
haematoma, 161
sequestrum, 294
Erythema multiforme, 247
Erythrocytosis, 255
Erythroplakia, 36, 37t, 40
Eugenol, zinc oxide and, effects on tooth, 312
Ewing's sarcoma, 79–80, 94, 298, 298b
Exfoliative cytology, 530–532, 535
Exophthalmic goitre, 393
External resorption of teeth, 343–345
Extraction wound healing, 354–355
complications of, 355
Extravasation mucous, 178

F

Facial clefts, 12
Facial hemiatrophy, 15
Facial hemihypertrophy, 15
Facial neuralgia, 80
Facial pain, 308t, 510–511
Facial paralysis, 114, 412, 505
Familial benign pemphigus, 453, 462, 466–467
Familial fibrous dysplasia of jaws, 424
Fanconi's syndrome, 37t
Fibroma, 56, 81, 147
ameloblastic, 141–142

cementifying, central, 433t
chondromyxoid, 81, 148
giant cell, 56–57
odontogenic, 147
ossifying, 57
Fibromatosis gingivae, 247
Fibro-osteoma, central, 57
Fibrosarcoma, 74–75, 93, 152–153
ameloblastic, 152–153
odontogenic, 152
Fibrous dysplasia of bone, 433t
craniofacial, 434
monostotic, 433
polyostotic, 434
Fibrous healing of extraction wound, 355, 356–357
Fibrous histiocytoma, 75–76
Fibrous union of fractures, 358
Filling materials, effects on tooth, 312
amalgam, 312
composite resins, 423
zinc oxide and eugenol, 312
zinc phosphate cement, 312
Fissured tongue, 6
Florid cemento-osseous dysplasia, 437
Fluorine, dental caries and, 259t, 271–272t
enamel hypoplasia and, 26–30
mottled enamel, 29

Foam cells, 371, 373
Focal epithelial hyperplasia, 377
Focal infection, 308–309
Focal reversible pulpitis, 280
Focus of infection, 308, 309
Folic acid, 382–383
Follicular cyst, 159
Foot-and-mouth disease, 207
Fordyce's granules, 13, 30
Forensic odontology, 516–523
Fournier's molars, 28, 30
 Fracture healing, 357–359
Fracture, mandibular condyle, 438
Frey's syndrome, 507–508, 508f, 515
Fungal infections, 183–233
 blastomycosis, 224–226
 botryomycosis, 191b, 192–193
 candidiasis, 220
 coccidioidomycosis, 227
 cryptococcosis, 229, 231t
 Darling's disease, 229
 histoplasmosis, 228–229
 moniliasis, 220
 mucormycosis, 231
 paracoccidioidomycosis, 226
 phycomycosis, 231
 thrush, 220

Fusion of teeth, 23

G

Galvanism, 37, 280
Gamma rays, 324
Gangrene of pulp, 324
Gardner's syndrome, 16, 17b, 146
Gaucher's disease, 371, 373–374
Gemination of teeth, 18
Genodermatoses, 445–477
Geographic tongue, 7, 459b
German measles, 12, 213
Ghost cells, 145, 168
Ghost teeth, 26
Giant cell fibroma, 55–57
Giant cell granuloma, 58–59
 central, 59
 peripheral, 58–59
Giant cell tumour of bone, 59
Gigantism, 5, 391
Gilchrist's disease, 225–226
Gingiva, fibromatosis, 14
 hyperplasia of, 244–245
 inflammation, 236, 322–323
Gingival cyst, of the adult, 157, 165–166
 of the newborn, 162
Gingival hyperplasia, 64, 244–245

Crohn's disease, 384, 246
dilantin sodium, 333
fibromatosis, 14
fibrous, 56
inflammatory, 243
leukaemia, 492
vitamin C deficiency, 246
Gingivectomy, healing, 245
Gingivitis, 236, 237, 241
acute necrotizing ulcerative, 239–240, 248
aetiology, 241
chronic desquamative, 238, 247
plasma cell, 241
Gingivostomatitis, 204, 240
Glandular fever, 491
Glass ionomer cement, effects on tooth, 312
Glossitis, 7, 482
Hunter's, 384, 482
interstitial, 196
syphilitic, 540–544t
Glossodynia, 507
Glossopharyngeal neuralgia, 505
Glossopyrosis, 507
Glucan, dental plaque and, 255
Goitre, exophthalmic, 393
Goltz–Gorlin syndrome, 31, 448–449
Gonorrhoea, 197–198

Gorlin cyst, 167
Gorlin–Goltz syndrome, 157, 448–449, 550f
Granulocytopenia, 420, 489
Granuloma, 57, 58–59, 198–199, 370, 412–413
 eosinophilic, 370
 giant cell, 58–59
 inguinale, 198–199
 midline lethal, 414
 periapical, 186, 287
 pyogenic, 201–203
 Wegener's, 412–413
Grinspan syndrome, 455
Ground-glass appearance of bone, 435
Gumma, 540–544t

H

Haemangioma, 8, 61
Haematoxylin, 528–529
Haemolytic anaemia, 208, 480, 483–484
Haemophilia, 499
Haemopoiesis, 375
Hailey–Hailey disease, 453, 466
Hair-on-end appearance of bone, 484, 486
Hairy tongue, 7, 332
Hamartoma, 8, 61, 167–168, 537
Hand-foot-and-mouth disease, 207, 540–544t
Hand–Schuller–Christian disease, 370, 372, 403

Hansen's disease, 188–190
Healing of wounds, 349–360
 after biopsy, 321
 after extraction, 354
 factors affecting, 351–352
Heck's disease, 14
Heerfordt's syndrome, 411, 414
Henderson–Patterson bodies, 232
Hereditary ectodermal dysplasia, 445
Hereditary enamel dysplasia, 23–24
Herpangina, 540–544t, 545t
Herpes simplex virus (HSV) infection, 204
Herpes zoster, 208
Herpetic whitlow, 206
High-speed instrumentation, effects on tooth, 311
Histiocytoma, fibrous, 75–76
 malignant, 75–76
Histiocytosis X disease, 370
 eosinophilic granuloma of bone, 370
 Hand–Schuller–Christian disease, 370
 Letterer–Siwe disease, 370
Histoplasmosis, 228–229
HIV (human immunodeficiency virus), 217, 232
HIV infection, oral manifestations of, 217
Hodgkin's disease, 76, 88–90
Howell–Jolly bodies, 482
Hunter's glossitis, 384, 482

Hurler syndrome, 369t, 370, 403
Hutchinson's teeth, 26, 28, 30
Hutchinson's triad, 28, 196
Hyaline bodies, 174, 457
Hyaluronidase, 43
Hypercementosis, 345–346
Hyperparathyroidism, 396–398
Hyperpigmentation, 453, 473
Hyperplastic pulpitis, chronic, 282–283
Hyperthyroidism, 393–395, 403
Hypertrophy, muscle, 514
Hypoparathyroidism, 396, 397–398
Hypophosphatasia, 363
Hypopituitarism, 392–393
Hypothyroidism, 394

I

Iatrogenic injury, 320
Identification in disasters, 520
Impacted teeth, 22–23, 344
Incisive canal cyst, 169, 170b
Infectious mononucleosis, 204, 491–492
Inflammatory papillary hyperplasia, 322, 323–324
Infratemporal space, infection in, 305t
Intestinal polyposis, 12
Intradermal naevus, 34
Intramucosal naevus, 34, 35

Intrinsic factor, 43, 384, 481
Involucrum, 292f, 294
Iron deficiency anaemia, 43, 480–481

J

Jaffe's fibrous dysplasia, 434
Jaw cyst, 155
Jaw lymphoma, African, 87–88
Junctional naevus, 34, 35, 93
Juvenile periodontitis, 249, 432

K

Kanamycin, dental caries, 271–272t
Kaposi's sarcoma, 77–79, 204, 218–219
Keratoacanthoma, 33–34, 540–544t
Keratocyst, odontogenic, 141, 156–159
Keratosis follicularis, 452–453
Kissing disease, 491
Klestadt's cyst, 170–171
Klinefelter syndrome, 399, 493
Koplik's spots, 210–211
Kveim–Siltzbach test, 411
Kwashiorkor, 199, 367

L

Lacunar cell, 345
Laser radiation, 311

Lateral periodontal abscess, 164, 251–252
Lateral periodontal cyst, 138, 163–164
LE (lupus erythematosus) cell, 475
Lead, effects on oral tissues, 338
Lead line, 329, 330
Leiomyoma, 68–69
Leiomyosarcoma, 90, 93
Lentigo maligna, 53
Leong's premolar, 19
Leontiasis ossea, 422, 434
Leprosy, 188–190
Lethal granuloma, midline, 414
Letterer–Siwe disease, 370, 372–373
Leukaemia, 73, 246, 492–495
Leukocytosis, 80, 491
Leukoedema, 13, 449
Leukopenia, 488–489, 491
Leukoplakia, 36, 451
Lichen planus, 455
Lichenoid reactions, 353, 457
Liesegang rings, 141
Lingual thyroid nodule, 540–544t
Lip biting, 319, 321
Lip, carcinoma, 10
 cheilitis glandularis, 10–11
 cheilitis granulomatosa, 321
 cleft, 10, 12

double, 10
pits, 10
Lipid metabolism, 370–374
disturbances in, 374–391
eosinophilic granuloma, 370
Gaucher's disease, 373–374
Hand–Schuller–Christian disease, 370
histiocytosis X disease, 370
Letterer–Siwe disease, 372–373
Niemann–Pick disease, 374
Lipoma, 60–69
Liposarcoma, 76–77
Lip prints, 517–518
Lipschutz bodies, 206, 232
Liquefaction foci, 268
Lobstein's disease, 415
Lock jaw, 193–194
Ludwig's angina, 306, 309
Lues, 194–197
Lupus erythematosus, 239
discoid, 472, 473–474
systemic, 469
Lupus vulgaris, 185
Luxation of temporomandibular joint, 440, 447
Lyell's disease, 462
Lymphangioma, 61, 65–66

M

Macrocheilia, 65
Macrodontia, 17–18
Macroglossia, 5, 15, 514
Macrognathia, 15
Malabsorption syndrome, 480
Malassez, rests of, ameloblastoma and, 128–129
 apical periodontal cyst and, 171
 lateral periodontal cyst and, 163
 odontogenic cysts and, 134
 squamous odontogenic tumour, 138–139, 139f
Malignant ameloblastoma, 149–150
Malignant lymphoma, 7, 88–90, 229
 African jaw, 87–88
 Burkitt's, 87–88
 Hodgkin's disease, 88–90
 non-Hodgkin's, 85
Malignant melanoma, 35, 84, 99
Malignant pleomorphic adenoma, 96, 100
Malocclusion, classification of, 391
Mandibulofacial dysostosis, 427–428
Marble bone disease, 419
Marfan syndrome, 417
Marie and Sainton's disease, 430
Maxillary sinusitis, 307–308
Measles, 203, 210
Median palatine cyst, 170b

Median rhomboid glossitis, 7, 221t
Melanotic macule, 11
Melkersson–Rosenthal syndrome, 11, 30, 238
MEN syndrome, 5
Mercury, effects on oral tissues, 329–330
Mesiodens, 17, 344
Metastatic tumours of jaws, 294
Microbial plaque, *See also* Dental plaque
 dental caries and, 247, 253–276
 periodontal disease, 248
Microdontia, 17
Microglossia, 5
Micrognathia, 14–15, 419
Midline lethal granuloma, 414
Miescher's syndrome, 11, 30
Mikulicz's disease, 120, 121
Miliary tuberculosis, 184
Miller's theory of dental caries, 253–257
Mineral metabolism, 361–367, 416
Molluscum contagiosum, 204, 213
Mongolism, 431
Moniliasis, 220
Monro's abscess, 459
Moon's molars, 28, 30
Mottled enamel, 26–30
Mouthwashes, dental caries, 239
Mucocele, 178–180

extravasation, 178
retention, 178f
Mucoepidermoid carcinoma, 95, 108–111
Mucopolysaccharide keratin dystrophy, 323
Mucormycosis, 229
Mucous retention cyst, 10, 97, 178
Mulberry molar, 26, 28, 30
Multiple myeloma, 83–84
Mummery, pink tooth of, 343–345
Mumps, 97, 216
Muscles, diseases of, 511
atrophy, 512
dystrophies, 511–512
hypertrophy, 514
Muscular dystrophies, 511–512
Muscular hypertrophy, 514
Myasthenia gravis, 513
Mycobacterium bovis, 184
Mycobacterium leprae, 188
Mycobacterium tuberculosis, 184, 219
Myeloma, 79–80, 83–84
Myoepithelial islands, 120, 121
Myoepithelioma, 96, 101
Myositis, 512–513
Myotonias, 512
Myxoedema, 394, 395
Myxoma, odontogenic, 147–148

N

Nasmyth's membrane, 257
Nasoalveolar cyst, 170–171
Nasolabial cyst, 170–171
Nasopalatine duct cyst, 169–170
Natal teeth, 22, 30
Necrosis, gangrenous, of pulp, 284
Necrotizing sialometaplasia, 111, 117–118
Necrotizing ulcerative gingivitis, acute, 239–240
Neonatal line, 28, 262t
Neonatal teeth, 22, 30, 198
Neuralgia, atypical facial, 503–504, 510
 glossopharyngeal, 505
 tic douloureux, 503
 trigeminal, 503–504
Neuroblastoma, 80, 86, 298b
Neuroectodermal tumour, 79
Neurofibroma, 70–71
Neurofibromatosis, 71–73
Neurofibrosarcoma, 92–93
Neuroma, traumatic, 69–70
Neutropenia, cyclic, 405, 489–490
Neutrophilia, 491
Naevus, 34, 449
 acquired, 34
 blue, 34
 compound, 34, 35

congenital, 5
intramucosal, 34, 35
junctional, 34, 35
spindle cell, 35
white sponge, 449
Niacin, 378–380
Nicotinic acid, 378
Niemann–Pick disease, 371, 374
Night grinding, 313
Nikolsky's sign, 463, 465, 466
Noma, 200, 212
Non-Hodgkin's lymphoma, 85–86, 218
Nonunion of fractures, 358
North American blastomycosis, 224–226
Nursing bottle caries, 262t

O

Ocular pemphigus, 468
Odontogenic adenomatoid tumour, 136–138
Odontogenic cysts, 131, 155–156
Odontogenic fibroma, 129, 147
Odontogenic keratocyst, 134, 156–159
Odontogenic myxoma, 129, 147–148
Odontogenic tumours, 127–153
Odontoma, ameloblastic, 143–144, 537
ameloblastic fibro-odontoma, 143–144
complex, 144, 537

composite, 19
Oncocytes, 103
Oncocytoma, 98, 103
Oncocytosis, 97, 103
Oral candidiasis, 78, 220
Oral-facial-digital syndrome, 6
Oral hairy leukoplakia, 218
Oral manifestations of HIV infection, 218
Oral melanotic macule, 198
Oral squamous cell carcinoma, 43–44
Oral submucous fibrosis, 36, 41–43
Orthodontic tooth movement, effects of, 318–319
Ossifying fibroma, central, 57
peripheral, 57
Osteitis deformans, 345, 421
Osteoarthritis of temporomandibular joint, 441
Osteochondroma, 66
Osteoclastoma, 176
Osteodentine, 340
Osteogenesis imperfecta, 24, 415–417
Osteoid osteoma, 67–68
Osteoma, 57, 67–68
Osteomalacia, 389
Osteomyelitis, 291–299
Osteopetrosis, 419–421
Osteoporosis circumscripta, 423
Osteoradionecrosis, 326–328

Osteosarcoma, 80, 82–83
Oxyphilic adenoma, 103–104

P

Pachyonychia congenita, 450, 476
Paget's disease of bone, 292, 296, 346
Palatal rugae, 517, 523
Palate, cleft, 5, 12–13, 344, 428
Pantothenic acid, 374, 380–381
Papillary cystadenoma lymphomatosum, 101–103
Papilloma, 106–107
 ductal, of salivary glands, 107
Papillomavirus, 215
Papillon-Lefevre syndrome, 250–251, 252
Paracoccidioidomycosis, 226, 232
Paradental cyst, 156, 172
Parathyroid gland, 395–398
 hyperfunction, 433
 hypofunction, 486
Parotid space, infection in, 303–305t
Parotitis, 197, 216
Parry–Romberg syndrome, 15
Pathologic calcification, 364
Peau d'orange pattern of bone, 435
Peg lateral incisor, 17
Pellagra, 378, 403
Pellicle, 258

Pemphigoid, benign mucous membrane, 241, 468f
bullous, 467, 468
cicatricial, 241, 468–469
Pemphigus, 453, 462, 538
Brazilian, 465
familial benign chronic, 453, 462
foliaceus, 462, 464–465
ocular, 469
vegetans, 462, 464
vulgaris, 271–272t, 462, 464f
Periapical abscess, 277f, 286–287, 289–290
Periapical cemental dysplasia, 438
Periapical cyst, 171–174, 291
Periapical granuloma, 287
Pericoronitis, 242–243, 252
Periodontal abscess, lateral, 164, 251–252
Periodontal cyst, 163
Periodontal pockets, classification, 171
Periodontitis, 235, 247, 285
Periostitis ossificans, 297
Peripheral giant cell granuloma, 58–59
Pernicious anaemia, 384, 481
Peutz–Jeghers syndrome, 12
pH, dental plaque and, 260, 537
saliva and, 260
Philadelphia chromosome, 494t
Phlegmon, 300

Phosphorus, 362, 403
Phycomycosis, 231
Pierre Robin syndrome, 14, 428–429
Pigmentation of teeth, erythroblastosis fetalis and, 487, 502
Pindborg tumour, 139
Pink disease, 330
Pink tooth of Mummery, 345, 348
Pioneer bacteria, 268
Pit and fissure caries, 262t, 269–270t
Pit and fissure sealant, dental caries, 271–272t
Pits and fistulas of lip, 10
Pituitary dwarfism, 17, 392, 403
Pituitary gigantism, 15, 18
Pityriasis rosea, 309, 459
Plasma cell gingivitis, 241
Plasmacytoma, 83
Pleomorphic adenoma, 96, 99–100
Plumbism, 329, 334
Plummer–Vinson syndrome, 44, 481
Polycythemia vera, 486–487
Polymyositis, 119
Polyostotic fibrous dysplasia of bone, 433
Port-wine stain, 63
Preauricular pits, 10
Pregnancy tumour, 202
Primordial cyst, 156
Proliferative periostitis, 297

Proteolysis-chelation theory of dental caries, 253–258
Proteolytic theory of dental caries, 257
Pseudohypoparathyroidism, 16, 398
Psoriasis, 458–459
Pterygomandibular space, infection in, 303–305t
Ptyalism, mercury, 124, 330
Pulp, abscess, 277–299
 aerodontalgia, 279b
 calcification, 268, 340–343
 chronic perforating hyperplasia, 279, 282
 denticles, 341
 hyperaemia, 279, 286
 polyp, 282
 stones, 25, 340
Pulpitis, 277f
 acute, 277f
 anachoretic, 186
 chronic, 279b
Purpura, thrombocytopenic, 496
Pyridoxine, 374, 381

Q

Queyrat, erythroplasia of, 40
Quincke's oedema, 413

R

Radiation, dental caries and, 265

laser, 311
X-ray, 208, 326
Radiation caries, 265, 326
Radicular cyst, 171
Ramsay Hunt syndrome, 209, 505
Ranula, 103, 179–180
Raspberry tongue, 183, 540–544t
Ray fungus, 191–192
Raynaud's phenomenon, 119, 476
Recurrent aphthous stomatitis, 219, 405
Recurrent dental caries, 262t, 264
Recurrent herpetiform ulcers, 407
Reed-Sternberg cell, 89, 94
Regional odontodysplasia, 26
Reiter's syndrome, 409–410, 414
Rendu–Osler–Weber syndrome, 61, 63–64
Residual cyst, 156, 171
Resorption of teeth, 343–345
Rests of Malassez, odontogenic tumours, 128–129
odontogenic cysts, 174
Rests of Serre, 128, 140, 156
Retention cyst, mucous, 97, 177t, 178f
of maxillary sinus, 155
Reticuloendotheliosis, lipid and nonlipid, 370
Rhabdomyoma, 69
Rhabdomyosarcoma, 90
Rhagades, 196

Rheumatoid arthritis, 441
Rh factor, 483, 487
Rhodamine, 187
Riboflavin, 377–378, 403
Rickets, 363, 388–389
Rodent ulcer, 51–52
Romberg syndrome, 15
Rootless teeth, 25
Root resorption, 62, 285, 359, 425
Root surface caries, 255t, 276
Rubinstein–Taybi syndrome, 20
 talon cusp, 20
Rushton bodies, 182
Russell bodies, 84, 288

S

Saber shin, 196
Saddle nose, 196, 412
Safety-pin cells, 199
Salivary duct cyst, 540–544t
Salivary glands, aberrancy, 9–10, 95
 agenesis, 9
 aplasia, 9
 atresia of ducts, 10
 chronic sialadenitis, 123
 mucocele, 155
 mumps, 216

parotitis, 123, 216
ranula, 97, 103
retention cyst, 178
sialadenoma papilliferum, 98, 106–107
sicca syndrome, 118–120
Sjogren's syndrome, 119
tumours of, 99–107, 108–117
acinic cell carcinoma, 114–115, 117
adenoid cystic carcinoma, 111b
basal cell adenoma, 104
canalicular adenoma, 105
clear cell adenoma, 105
cylindroma, 111–113
ductal papilloma, 106–107
inverted, 107
lymphoepithelial lesion, benign, 121
malignant, 115
Mikulicz's disease, 120
mucoepidermoid carcinoma, 108–111
necrotizing sialometaplasia, 117–118, 126
oncocytoma, 103–104
oxyphilic adenoma, 103–104
pleomorphic adenoma, 99–101, 115–116
Warthin's, 101–103
xerostomia, 124–125
Sarcoidosis, 97, 161–162
Sarcoma, ameloblastic, 152–153, 540–544t

chondrosarcoma, 80–81
Ewing's, 79–80
fibrosarcoma, 74–75
Kaposi's, 77–79
leiomyosarcoma, 90
liposarcoma, 76–77
neurofibrosarcoma, 92–93
osteosarcoma, 81
rhabdomyosarcoma, 90
Saw tooth rete pegs, 457
Scarlet fever, 27, 183–184
Schwannoma, malignant, 92–93, 99
Scleroderma, 475–476
Sclerosing osteomyelitis, chronic diffuse, 296–297
Scrofula, 186, 231
Scrotal tongue, 6, 432
Scurvy, 246, 385
Sequestrum, 294, 327
Sex determination, 522
Shell teeth, 25
Shingles, 207
Sialadenitis, chronic nonspecific, 122
Sialadenoma papilliferum, 98, 106–107
Sialolithiasis, 122–123
Sicca syndrome, 118–120
Sickle cell anaemia, 3, 483
Simple bone cyst, 174, 318

Sinusitis, maxillary, acute, 307
chronic, 177
Sjogren's syndrome, 118–120
Smallpox, 213
Smooth surface caries, 264
Solitary bone cyst, 174–176, 318
South American blastomycosis, 226
Speckled leukoplakia, 38, 545t
Sphingomyelin metabolism disturbance, 371
Spindle cell naevus, 92
Squamous cell carcinoma, 43–47, 151–152, 161
of buccal mucosa, 43, 48
of floor of mouth, 43, 94
of gingiva, 43, 49
of lip, 43, 47
of palate, 43, 49
of tongue, 43, 47–48
Squamous odontogenic tumour, 129, 138–139
'Starry sky' appearance, 87
Stevens–Johnson syndrome, 461
Stomatitis, denture, 221t
Strawberry tongue, 183
Streptococcus mutans, 254, 260
Striae of Wickham, 455, 456, 540–544t
Sturge–Weber syndrome, 61, 62, 64–65
Subluxation of temporomandibular joint, 440
Sublingual space, infection in, 303–305t, 306

Submandibular space, infection in, 303–305t
Submental space, infection in, 303–305t, 306
Submerged tooth, 23
Submucous fibrosis, 36, 41–43
Sulphur granules, 191
Superficial spreading melanoma, 52, 54
Supernumerary roots, 18, 54
Supernumerary teeth, 16–17
Sutton's disease, 504
Swift's disease, 330
Swiss cheese pattern, 112
Syndrome, 9, 84, 221t, 250–251, 540–544t
 AIDS, 9, 77, 216, 251, 540–544t
 Albright's, 434
 Apert, 426–427
 basal cell naevus, 181, 550f
 Beckwith–Wiedemann, 5, 15, 29
 bifid rib, 158
 Chediak–Higashi, 490–491
 CREST, 476
 Crouzon, 426
 Cushing's, 402
 Down, 431–432
 Ehlers–Danlos, 340, 447–448
 Ellis–van Creveld, 430, 446–447
 Frey's, 507–508
 Gardner's, 16, 146

Goltz-Gorlin, 448–449
Grinspan, 455
Heerfordt's, 411, 414
hereditary intestinal polyposis, 12
Klinefelter, 399, 493
Marfan, 415b, 417–418, 444
Melkersson-Rosenthal, 6, 11, 30, 545t
MEN, 5
Miescher's, 11
oral-facial-digital, 6
Papillon–Lefevre, 250–251, 252
Parry–Romberg, 15
Peutz–Jeghers, 12
Plummer–Vinson, 481, 502
Ramsay Hunt syndrome, 209, 232
Reiter's, 409–410, 414
Rubinstein–Taybi, 20
SAPHO, 296
sicca, 118–120
Sjogren's, 118–120
Stevens–Johnson, 461
Treacher Collins, 427
trisomy, 431–432
van der Woude's, 3, 10, 30
Syphilis, 27, 28, 44, 194–197
Systemic sclerosis, 475–476

T

Talon cusp, 20
Target cells, 406f
Target lesions, 461
Taurodontism, 21
Telangiectasia, haereditary hemorrhagic, 63–64
Temporomandibular joint disease, 438–444
 ankylosis, 440–441
 aplasia of condyle, 438
 dislocation, 440
 luxation, 440
 subluxation, 440
Tertiary dentine, 339
Tetanus, 193–194
Tetracycline, dental caries, 271–272t, 332–333
Thalassaemia, 486
Thiamin, 375–376
Thistle tube pulp, 26
Thrombocytopenic purpura, 495
Thrush, 220
Thyroglossal duct cyst, 180
TNM classification, 45t
Tongue, aglossia, 5–7
 ankyloglossia, 6
 benign migratory glossitis, 7
 bifid, 158, 418
 central papillary atrophy, 221, 540–544t

erythema migrans, 460, 540–544t
fissured, 6
geographic, 7
glossodynia, 384
glossopyrosis, 7
macroglossia, 5
median rhomboid glossitis, 7
raspberry, 183, 540–544t
scrotal, 6, 11
strawberry, 183, 540–544t
Tongue tie, 6
Tonsil, lingual, 7
Tooth, abfractions, 335, 337
abrasion, 336–337
amelogenesis imperfecta, 21, 23–24
ankylosis, 313, 316
anodontia, 15–16
attrition, 335–336, 335f
bruxism, 313–314
cleidocranial dysplasia, 430–431
concrescence, 18
dens evaginatus, 19
dens in dente, 19
dens invaginatus, 19–20
dentine dysplasia, 23–24
dentinogenesis imperfecta, 24–25
deposits on, 11, 74b, 79

calculus, 237, 536
dental plaque, 245–246, 537
dental stains, 268
pellicle, 258
dilaceration, 20
ectodermal dysplasia, 92, 430
embedded, 22
enamel hypoplasia, 26–30
erosion, 337–338, 347
Fournier's molars, 28, 30
fractures, 314–315
fusion, 18
Gardner's syndrome, 16, 17b, 146
gemination, 18, 30
ghost, 26
hereditary opalescent dentine, 24
Hutchinson's, 28
impacted, 22–23
internal resorption, 283, 343
mesiodens, 16, 344
Moon's molars, 28, 30
mulberry molar, 28
natal, 22, 450
neonatal, 22, 320, 430
odontodysplasia, 26
orthodontic tooth movement, 318–319
peg lateral, 17

pellicle, 258
pigmentation, 330, 332
premature eruption, 22, 447
regional odontodysplasia, 26
rootless, 25
shell, 25
supernumerary, 16–17
talon cusp, 20
taurodont, 18, 21
Turner's, 26, 29
Toxic epidermal necrolysis, 16, 460
Transplantation of teeth, 343, 359
Traumatic cyst, 318
Traumatic neuroma, 69–70, 540–544t
Traumatic ulcers, 223, 321, 407
Treacher Collins syndrome, 427
Trench mouth, 239
Treponema pallidum, 194, 238
Trismus, 43, 303–305t, 314
Trisomy, 431–432
Trypsin, 287, 352
Tuberculoma, 186
Tuberculosis, 184–188
Tuberculum impar, 7
Tumours,
adenoid cystic carcinoma, 98, 111b
adenomatoid odontogenic tumour, 129, 136, 138

African jaw lymphoma, 87–88
ameloblastic carcinoma, 150
ameloblastic dentinosarcoma, 143, 153
ameloblastic fibroma, 141
ameloblastic fibro-odontoma, 129, 143–144
ameloblastic fibrosarcoma, 129, 152–153
ameloblastic sarcoma, 152
ameloblastoma, 129
basal cell adenoma, 104
basal cell carcinoma, 50, 111b, 185
benign cementoblastoma, 149
Burkitt's lymphoma, 87–88
calcifying epithelial odontogenic tumour, 129, 139–141
canalicular adenoma, 98, 105
cementoma, 149, 438
chondroma, 66
chondrosarcoma, 80–81
cylindroma, 111–113
ductal papilloma, 106
epidermoid carcinoma, 43, 108
Ewing's sarcoma, 79, 298b
fibrosarcoma, 74
giant cell fibroma, 55–57
giant cell granuloma, central, 58–59
 peripheral, 58–59
haemangioma, 61
histiocytosis X, 370

Hodgkin's disease, 76, 88–90
Kaposi's sarcoma, 77–79
keratoacanthoma, 33–34
leiomyoma, 68–69
leiomyosarcoma, 90
leukoedema, 13, 449
leukoplakia, 36
lipoma, 60–69
liposarcoma, 76–77
lymphangioma, 65–66
malignant ameloblastoma, 149–150, 153
malignant melanoma, 35, 99
mucoepidermoid carcinoma, 95, 108–111
myeloma, 79–80, 83–84
myxoma, 129, 147–148
neurofibroma, 70–71
neurofibromatosis, 71
neuroma, 69–70
non-Hodgkin's lymphoma, 85–86
odontogenic myxoma, 147
odontoma, 153
oncocytoma, 103
osteoclastoma, 176
osteosarcoma, 81
oxyphilic adenoma, 103–104
papilloma, 106
Pindborg tumour, 139

pleomorphic adenoma, 99–101
rhabdomyoma, 69
rhabdomyosarcoma, 90–92
schwannoma, 72
sialadenoma papilliferum, 35, 106–107
squamous cell carcinoma, 43–47
squamous papilloma, 31–32
squamous odontogenic tumour, 129, 138–139
traumatic neuroma, 69–70
true cementoma, 149
verrucous carcinoma, 50–51
von Recklinghausen's disease of skin, 71
Warthin's tumour, 95, 101–103
Turner's teeth, 29, 30
Tzanck cells, 207, 463
Tzanck test, 206–207, 209, 464

U

Ulcer, traumatic, 223, 321
Unerupted teeth, multiple, 16
Unicameral bone cyst, 174, 176, 318

V

Vancomycin, dental caries, 271–272t
van der Woude's syndrome, 3, 10, 30
Varicella Zoster virus, 204, 207
Variola, 213

Verocay bodies, 73
Verruca vulgaris, 32–33
Verruciform xanthoma, 540–544t
Verrucous carcinoma, 50–51, 544t
Vincent's infection, 239, 461
Viral infections, 123, 203, 219, 408
 Behcet's syndrome, 408–409, 540–544t
 cat scratch disease, 200–201
 chickenpox, 207–208
 cytomegalic inclusion disease, 204
 German measles, 213
 herpes simplex, 204–207, 219
 herpes zoster, 208
 HIV infection, 216
 measles, 210
 molluscum contagiosum, 214
 mumps, 216
 oral candidiasis, 220, 400
 Reiter's syndrome, 409–410, 414
 rubeola, 203, 210–211
 shingles, 207
 smallpox, 213
 varicella, 207
 variola, 213
Vitamin A, 27, 261, 351, 386–387
 deficiency of, 351, 386–387
 enamel hypoplasia, 27

Vitamin B complex, 374, 481
Vitamin B_1 (thiamin), 374
Vitamin B_2 (riboflavin), 374, 377–378
Vitamin B_3 (niacin), 374, 378–380
Vitamin B_5 (pantothenic acid), 374, 380–381
Vitamin B_6 (pyridoxine), 374, 381
Vitamin B_8 (biotin), 374, 381–382
Vitamin B_9 (folic acid), 374, 382–383
Vitamin B_{12} (cyanocobalamin), 374, 383–384
Vitamin C, 246
deficiency of, 246
enamel hypoplasia, 27
Vitamin D, 387–389
deficiency of, 125, 388–389
enamel hypoplasia, 27
osteomalacia, 387
rickets, 387
Vitamin E, 375, 389–390
Vitamin K, 271–272t, 375, 390–391
von Recklinghausen disease, 71
von Willebrand disease, 501

W

Warthin's tumour, 95, 101–103
Wegener's granulomatosis, 412–413, 414
White sponge naevus, 449

Whitlow, herpetic, 206
Wickham's striae, 456, 540–544t
Wound healing, 219, 352–353
 after biopsy, 321
 after extraction, 354
 factors affecting, 351–352

X

Xanthoma, verruciform, 540–544t
Xeroderma pigmentosum, 36, 93
Xerostomia, 118, 124, 265
 Sjogren's syndrome, 118–120
X-ray radiation, 208, 326, 439
 aplastic anaemia, 482
 bone, effects on, 326
 extraction wound healing, 354–355
 oral mucosa, effects on, 325
 salivary glands, effects on, 326
 teeth, effects on, 326
 wound healing, 352–353
 xanthoma, verruciform, 540–544t
 xerostomia, 325, 326

Z

Zinc, 361
Zinc oxide and eugenol, effects on tooth, 312
Zinc phosphate cement, effects on tooth, 312